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La transdisciplinarité dans le champ des troubles des conduites alimentaires : un modèle innovant pour le soin et la recherche

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Corinne Blanchet. La transdisciplinarité dans le champ des troubles des conduites alimentaires : un modèle innovant pour le soin et la recherche. Psychologie. Université Paris Cité, 2019. Français. NNT : 2019UNIP5172 . tel-04003501

HAL Id: tel-04003501

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Université de Paris

École doctorale ED 261

« Cognition, Comportements, Conduites Humaines »

Laboratoire de Psychologie Clinique, Psychopathologie, Psychanalyse (PCPP)

La transdisciplinarité dans le champ des troubles des conduites alimentaires Un modèle innovant pour le soin et la recherche

Par Corinne Blanchet

Thèse de doctorat de psychologie

Dirigée par le Professeur Marie Rose Moro

Présentée et soutenue publiquement le 11 Décembre 2019

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Titre

La transdisciplinarité dans le champ des troubles des conduites alimentaires : un modèle innovant pour le soin et la recherche

Résumé

La transdisciplinarité est un concept issu des sciences humaines, introduit en France par Jean Piaget en 1970, appartenant au monde de la “pensée complexe”. La transdisciplinarité, fait suite à l’explosion des savoirs et à l’exigence de réunification des disciplines autour d’un même objet dans le domaine des sciences. Dans le domaine de la santé, il répond à la nécessité d’approches disciplinaires multiples et de regards croisés autour du patient. Le champ des Troubles des Conduites Alimentaires (TCA), s’est historiquement construit autour du sujet anorexique et de la compréhension étiopathogénique du trouble, avec le développement d’approches mono/pluri/interdisciplinaires, puis, en ce début de 21^{ème} siècle, d’approches intégratives associées à un modèle biopsychosocial du TCA. Le terme de transdisciplinarité, sorte de « concept nomade », terme polysémique, régulièrement dévoyé, a progressivement envahi le langage des professionnels et intervenants impliqués dans le champ des TCA, mais reste peu exploré et insuffisamment utilisé dans ce champ. Notre travail de recherche, incluant une étape d’analyse conceptuelle ainsi qu’une approche épistémologique, s’est attaché à décrire en quoi le champ des TCA est “transdisciplinaire” et comment le concept de transdisciplinarité est utile pour en comprendre l’organisation actuelle des soins et de la recherche. Nous proposons une première modélisation théorique du système que représente la nécessaire transdisciplinarité dans le champ de l’anorexie mentale. Ce modèle décrit les différents acteurs impliqués, leurs interactions, et les différents concepts qui circulent dans cet espace complexe des TCA. La transdisciplinarité dans le champ des TCA apparaît comme un nouveau paradigme, à la fois rupture épistémologique et nouvel espace de pensée complexe, réconciliant connaissance, savoir et pratique médicale. Ce modèle innovant d’approche humaniste et intégrative ouvre de multiples perspectives, pour le sujet souffrant de TCA, et en particulier pour les adolescents, dans les domaines du soin et de la recherche.

Mots Clefs

Transdisciplinarité, complexité, troubles des conduites alimentaires, anorexie mentale, médecine, sciences humaines, épistémologie, analyse conceptuelle, modélisation.

Title

Transdisciplinarity in the field of eating disorders: an innovative model for care and research

Summary

Transdisciplinarity is a concept stemming from the human sciences, introduced in France by Jean Piaget in 1970 and based on the "complex thought". Transdisciplinarity follows the explosion of knowledge and the need for gathering disciplines around the same object in the field of science and the need for multiple disciplinary approaches and cross-fertilization of views around the patient in the health field. The field of Eating Disorders (ED), was historically built around the anorexic subject, related to the etiopathogenic understanding of the disorder, with the development of mono-, multi-, or interdisciplinary approaches, then at the beginning of the 21st century, with the integrative approaches associated with a biopsychosocial model of ED. The term transdisciplinarity, a kind of "nomadic concept", a polysemic and regularly misused term, has gradually invaded the language of professionals and stakeholders involved in the ED field, but remains little explored and insufficiently used in this field. Our research work, including a conceptual analysis step and an epistemological approach, focused on describing how the field of ED is "transdisciplinary" and how the concept of transdisciplinarity is useful in understanding its current organization of care and research. We propose a project of theoretical modeling of the system that represents the necessary transdisciplinarity in the field of anorexia nervosa. This model describes the different actors involved, their interactions, and the different concepts that circulate in this complex ED space. Transdisciplinarity in the field of ED appears as a new paradigm, both an epistemological rupture and a new complex space of thought, reconciling knowledge, understanding and medical practice. This innovative model of a humanistic and integrative approach opens up multiple perspectives, for the subject suffering from ED, and in particular for adolescents, in the fields of care and research.

Key words

Transdisciplinarity, complexity, eating disorders, anorexia nervosa, medicine, humanities, epistemology, conceptual analysis, modeling.

A Nathan, mon fils,

A ma famille, à mes chers amis,

A Daniel, à David mes potos...

Remerciements

A Madame le Professeur Marie Rose Moro

Je vous remercie sincèrement de m'avoir donné l'opportunité de m'engager dans ce projet de thèse et de me faire l'honneur de diriger ce travail. Merci pour la confiance que vous m'avez toujours accordée, pour vos encouragements tout au long de ces années, et pour les nombreux projets que nous ne manquerons de construire dans l'avenir. Soyez assurée de mon profond respect.

A Monsieur le Professeur Olivier Bonnot, et Monsieur le Professeur Jean-Philippe Raynaud, vous me faites l'honneur de votre présence et de juger ce travail. Soyez-en sincèrement remerciés.

A Madame le Professeur Nathalie Godart

Merci pour ton accueil chaleureux et bienveillant dans "le champ des TCA" et pour toutes les portes entrouvertes au cours des quinze dernières années...Nos projets et travaux communs ont toujours été jubilatoires et enrichissants...même lorsqu'ils nous font veiller tard....le meilleur restant à venir... Sois assurée de ma profonde reconnaissance et de mon amitié sincère.

A Monsieur le Professeur Jean-Michel Oppert

Nous connaissons ce lien indéfectible qui nous unit depuis mon internat à l'Hôtel Dieu...C'est un honneur et un immense plaisir de te compter parmi les membres de ce jury. Sois assuré de mon amitié sincère.

À Alice Titia Rizzi

La plus Italienne des psychologues, qui me permet aussi de vivre ma part de transculturalité... merci pour nos échanges aussi riches que vivifiants, ta bonne humeur communicative et tes interventions percutantes auprès de nos jeunes patients...Je souhaite sincèrement que nous trouvions le temps de développer nos idées et d'avancer dans nos projets de recherche. Merci pour ton amitié.

A la mémoire du Professeur Jean-Pierre Luton

Qui fut mon Maître en Endocrinologie, qui m'a appris l'humilité, la rigueur, et le sens du devoir face aux patients et m'a permis précocement de porter mon regard au-delà du symptôme, m'ouvrant le chemin vers une médecine humaniste et transdisciplinaire.

Au Professeur Arnaud Basdevant

Mon Maître et ami, merci pour les valeurs que tu incarnes, et pour ce que tu m'as transmis. La Nutrition est un Humanisme...nous le savons... Sois assuré de mon profond respect et de mon engagement à défendre les valeurs communes que nous partageons.

Au Professeur Jean Wilkins

Mon Maître et ami, qui m'a fait l'honneur, au cours de mon Fellowship à Montréal, de partager sa passion pour "ces petites filles" anorexiques et a su voir en moi une possible relève outre-atlantique. Merci pour votre amitié, votre confiance et ces liens si précieux que nous avons su conserver au fil des années.

Au Professeur Marcel Rufo

Vous m'avez accordé votre confiance et permis d'embarquer dans cette singulière aventure...soyez assuré de ma profonde et éternelle gratitude.

A tous ces adolescent(e)s et leurs familles, croisé(e)s au cours de ces quinze années; nos rencontres continuent de me bouleverser et de me donner un élan sans cesse renouvelé qui a, entre autre, participé à la genèse de ce travail de thèse. Merci.

Merci à toute l'équipe de la Maison de Solenn, pour ces quinze incroyables années d'expériences professionnelles, d'échanges et de moments de vie partagés...

A Ruben, Gabriela et Martine...

Je souhaite remercier sincèrement l'équipe de l'ED 261 qui nous accompagne avec bienveillance et le laboratoire PCPP pour ouvrir ses portes à des chercheurs de tous horizons. Merci aux doctorants croisés durant ces années de thèse.

Merci à tous les membres de la FFAB, de la FNA-TCA et du Réseau TCA Francilien, vous qui incarnez aussi "le rêve transdisciplinaire"; puissent nos travaux en cours et projets se poursuivre dans cette ambiance chaleureuse et conviviale.

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LISTE des ABREVIATIONS

ANMDA : Association Nationale des Maisons des Adolescents

APA : American Psychiatric Association

CIM : Classification Internationale des Maladies

CIRET : Centre International de Recherche et Études Transdisciplinaires

DGOS : Direction Générale de l'Organisation des Soins

DSM : Diagnostic and Statistical Manual

ETP : Education Thérapeutique du Patient

FFAB : Fédération Française Anorexie Boulimie

HAS : Haute Autorité de Santé

MDA : Maison des Adolescents

NICE : National Institute for Health and Care Excellence

OMS : Organisation Mondiale de la Santé

TCA : Troubles des Conduites Alimentaires

WONCA : World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians

“ Toutes choses étant causées et causantes, aidées et aidantes, médiates et immédiates, et toutes s'entretenant par un lien naturel et insensible qui lie les plus éloignées et les plus différentes, je tiens impossible de connaître les parties sans connaître le tout, non plus que de connaître le tout sans connaître particulièrement les parties“.

Blaise Pascal (Pensées, 1670)

“ La pensée simple résout les problèmes simples sans problème de pensée. La pensée complexe ne résout pas d'elle-même les problèmes, mais elle constitue une aide à la stratégie qui peut les résoudre. Elle nous dit : “Aide-toi, la pensée complexe t'aidera”.

Edgar Morin (Introduction à la pensée complexe, 1990)

INTRODUCTION

INTRODUCTION

La réflexion épistémologique concernant la rencontre des disciplines dans les différents domaines des sciences, apparaît comme un phénomène récent, en lien avec la période de postmodernité de la société occidentale. Cette réflexion, émerge dans les années 1960 d'une aspiration vers un idéal d'unité de la connaissance, après des siècles de dogmatisme monodisciplinaire et de positivisme scientifique, héritages de l'idéologie cartésienne dominante, de construction disciplinaire, en médecine en particulier, par spécialisations qui furent nécessaires à l'acquisition des connaissances empiriques et au déploiement du savoir universitaire. Historiquement, la période de spécialisation médicale qui se développe en France à partir de la fin du 18^{ème} siècle au cours de la Révolution Française, opère un véritable bouleversement conceptuel évoluant de la théorie "humorale" à la théorie "tissulaire" par l'intermédiaire de Xavier Bichat (1771-1802) en particulier. Cette révolution de la rationalité médicale s'affirme dans la seconde moitié du 19^{ème} siècle avec la reconnaissance par les Facultés de Médecine, à Paris, et quelques grandes villes de Province, d'enseignements spécialisés à partir des années 1860-1880 (Weisz, 1994). Ainsi, la première chaire de clinique des maladies mentales naît elle en 1877 (Pinell, 2005 ; Couturier, 2009). L'oeuvre de Pierre Janet (1859-1947), philosophe et psychiatre, fondateur de la psychologie dynamique, demeure centrale dans le rapprochement des disciplines et par sa volonté d'unir la médecine et la psychologie. En profond désaccord avec les aliénistes du 19^{ème} siècle qui proposent une vision réductrice de la maladie mentale par la physiologie du système nerveux, il introduisit la psychologie dans les études médicales, afin d'aborder la dimension psychique de la maladie psychiatrique. Cette proposition visionnaire de Janet, encourageant les interactions entre médecine et psychologie dès la fin du 19^{ème} siècle, s'étendait plus largement à la rencontre

des sciences biologiques et des sciences humaines (Quetel, 2012). La période de l'après-guerre en France, avec la naissance de la *Sécurité Sociale* et du *Conseil de l'Ordre des Médecins*, connaît une rapide accélération puis une explosion du nombre de disciplines quelques décennies après les USA et d'autres pays Européens comme l'Allemagne, où la spécialisation des disciplines revêt un caractère essentiellement académique à visée de recherche et d'enseignement (Weisz, 2005). Ce mouvement, n'est pas uniquement relié à la progression du savoir et aux avancées scientifiques mais il apparaît également mû par des enjeux complexes d'ordre intellectuels, socio-professionnels, administratifs, économiques et politiques ; comme le souligne le sociologue Patrice Pinell "il y a tellement de causes possibles et probables (...) qui déterminent la spécialisation en médecine, que toute tentative d'en privilégier une ne peut que reposer sur des présuppositions métaphysiques relatives à la façon dont le monde fonctionne" (Weisz, 1994 cité par Pinell 2005, p 6). L'hyperspécialisation avec la naissance de "sous" ou "sur" disciplines et le cloisonnement du savoir font craindre un risque de déshumanisation de la médecine autour d'un objet morcelé et font redouter un isolement du chercheur. Le philosophe et sociologue Edgar Morin souligne un risque de "chosification de l'objet étudié dont on risque d'oublier qu'il est extrait ou construit" (Morin, 1994). Le processus de spécialisation, en modifiant la configuration du champ médical "tend à modifier les conditions mêmes de sa poursuite" (Pinell, 2005) et portait ainsi en lui-même ses propres limites annonçant l'avènement de l'histoire actuelle de la dialectique disciplinaire.

En France, l'avènement des idées pluridisciplinaires dans les années 1950-1970, contestant la pensée réductionniste contemporaine, introduit la nécessité de réunification des disciplines et marque l'évolution vers les courants de pensée holistes (Paul, 2001). Historiquement, cette période vient rompre avec les préceptes socio-culturels antérieurs dans tous les domaines de la vie humaine : la créativité culturelle, l'innovation artistique, la diffusion de l'enseignement des sciences et de la recherche. Les mouvements de la contre-culture anglo-saxonne nés aux USA et au Royaume-Uni, touchent à leur apogée entre 1965-1972 ; les tensions intergénérationnelles; les mouvements de contestation étudiantes et

sociales de “Mai 68” en France et la seconde vague des mouvements féministes émergent également dans les années 1970 en Europe et aux USA. Tous ces bouleversements remettent en cause les institutions traditionnelles de la société patriarcale et luttent pour le droit des femmes à disposer librement de leur corps. Cette période correspond également à des évolutions notables dans le domaine de l’enseignement supérieur et de la recherche avec la création de nouveaux programmes et des perspectives d’avenir pour les Universités du futur s’inscrivant dans une approche transdisciplinaire tels que décrit par l’astrophysicien Jantsch (Jantsch, 1972a, cité par Bernstein 2015, p3).

C’est dans ce contexte “d’indisciplinarité” et de rupture avec les idéologies passées, propice à l’explosion des savoirs, à l’apogée de l’hyperspécialisation disciplinaire et de la “médecine d’organe”, que les premières critiques adressées à la toute-puissance du travail monodisciplinaire amorcent la réflexion sur l’intérêt des rencontres entre disciplines, « l’interdisciplinarité pour sauver le monde” (Laflamme, 2011). Face aux risques inhérents au cloisonnement et au morcellement de la “modernité”, la seconde moitié du 20^{ème} siècle se voit ainsi mise au défi de procéder au décloisonnement des disciplines et d’envisager un nouveau modèle assurant harmonie, unité et globalité autour de l’objet. Favorisés par l’émergence de “la pensée complexe” et la remise en question de la vision pyramidale de la connaissance, de nombreux concepts émergent, faisant référence aux différents niveaux d’interactions entre disciplines notamment dans les domaines de la recherche, de l’enseignement (Gusdorf, 1983 ; Thompson Klein, 1990) et de la santé (Choi & Pak, 2006 ; Choi & Pak, 2007 ; Choi & Pak, 2008). Selon Edgar Morin “si l’histoire officielle de la science est celle de la disciplinarité, une autre histoire, qui lui est liée et inséparable, est celle des “inter-trans-poly-disciplinarités” (Morin, 1994). C’est dans ce contexte que le concept de transdisciplinarité émerge dans les années 1970 (Piaget, 1972), alors que les premiers projets transdisciplinaires ne verront le jour que vingt années plus tard.

Dans le domaine de la santé, la volonté de révolutionner les liens entre les disciplines et de promouvoir une approche globale, intégrée, orientée vers la famille et la communauté est illustrée par la loi cadre de l'Organisation Mondiale de la Santé (OMS) en 1998 et la proposition d'un modèle holistique par l'Organisation mondiale des médecins généraliste¹. En France, la reconnaissance et la valorisation des interactions disciplinaires sont illustrées par la récente Lois Santé 2016² qui vise à promouvoir l'interdisciplinarité comme clef de voute du parcours de soins, de santé, et de vie du patient, et favorisent le développement d'enseignements transversaux et la recherche translationnelle dans les universités. En médecine, historiquement les approches pluri-, inter- ou transdisciplinaires se sont développées pour des pathologies chroniques, lourdes, et instables comme les soins palliatifs (Pétermann, 2007), les déficits intellectuels de l'enfant (Pelletier, 2005) ou l'épilepsie sévère (Lisack & Hu-Berteaud, 2013). Des programmes d'Education Thérapeutique du Patient³ développés pour les pathologies chroniques somatiques (diabète, obésité), psychiatriques (trouble bipolaire, schizophrénie) ou neuro dégénératives (Alzheimer, Sclérose en plaques), et plus récemment pour les TCA, inscrits depuis Juillet 2009 dans la Loi Hôpital Patients, Santé Territoire⁴, illustrent le nécessaire développement des approches disciplinaires multiples coordonnées pour les pathologies chroniques et sont inscrites dans le parcours de soins du patient (de la Tribonnière & Gagnayre, 2013).

Les troubles des conduites alimentaires (TCA), pathologies chroniques d'origine polyfactorielle, émergeant majoritairement chez la fille à l'adolescence,

¹ La WONCA (acronyme signifiant World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians, souvent abrégé en World Organization of Family Doctors) est l'Organisation Mondiale des Médecins Généralistes.

² Loi santé 2016 de la Direction Générale de l'Offre de Soins (DGOS) (<https://solidarites-sante.gouv.fr/dgos-direction-generale-de-l-offre-de-soins>).

³ Programmes d'Education Thérapeutique pour le Patient-ARS IdF-(www.iledefrance.ars.sante.fr/education-therapeutique-du-patient).

⁴ Loi Hôpital Patients, Santé Territoire 2009 (HPST) (www.solidarites-sante.gouv.fr/IMG/pdf/vademecum_loi_HPST).

concernent toutes les tranches d'âge, tous les contextes socioculturels (Smink, Van Hoeken, & Hoek, 2012 ; Herpertz-Dahlmann, 2015) et constituent un véritable problème de santé publique avec une prévalence vie entière de 5 à 15 % dans les pays Occidentaux (Smink, 2012). Dans le champ des TCA, les stratégies thérapeutiques et la philosophie des soins ont subi des bouleversements profonds au cours du dernier siècle, parallèlement à l'évolution des modèles de compréhension étiopathogénique de ces troubles. Ces étapes faites de ruptures épistémologiques successives (Brusset, 1977), reflètent également les évolutions organisationnelles et socio-politiques médicales, ainsi qu'une réalité anthropologique représentée par l'évolution des subjectivités dans le milieu médical, la "révolte des usagers" et "l'autonomisation croissante du sujet dans la médecine contemporaine" particulièrement présente dans le champ des TCA en ce début de siècle (Klein, 2012). Que ce soit dans le cadre de l'approche théorique ou de l'approche clinique, les TCA bénéficient depuis quelques décennies et de façon exponentielle, des regards convergents et des compétences disciplinaires et professionnelles variées issues de champs épistémologiquement plus ou moins proches que sont les spécialités médicales du *soma* et de la *psyché*, mais également les neurosciences, la génétique et les sciences humaines et sociales. Dans le domaine du soin, les approches intégratives et coordonnées, qualifiées de "multidisciplinaires" ou "pluridisciplinaires" dans les guidelines internationaux font actuellement consensus (Haute Autorité de Santé, 2010 ; Haute Autorité de Santé, 2019 ; American Psychiatric Association, 2006 ; National Institute for Health and Care Excellence, 2017). Ces approches complexes, faisant intervenir dans différents contextes et selon différentes modalités une multitude de disciplines et de professionnels réunis autour du patient, sont désignées indifféremment par les mots pluri-, multi-, inter-, transdisciplinarité ; la distinction sémantique entre ces termes restant, le plus souvent, obscure. Le terme de transdisciplinarité apparaît, dans ce "bourbier sémantique" (Choi & Pak, 2003), comme un terme polysémique, interchangeable avec les termes de multi/pluri/interdisciplinarité. A notre connaissance, aucun article dans la littérature internationale ni aucun

travail de thèse doctorale ne semblent pas avoir rattaché le concept de transdisciplinarité à l'épistémologie des TCA, malgré une utilisation croissante de ce terme dans ce domaine.

Ce travail nous propose donc de partir à la rencontre de ce concept émergent de transdisciplinarité, qui a su éveiller notre curiosité, d'étudier sa légitimité dans le champ des TCA et ses applications dans le domaine du soin et de la recherche, et d'en évoquer les perspectives de modélisation dans ce champ. Cette démarche a été initiée dans le cadre de notre expérience institutionnelle, dans une "Maison des Adolescents", structure polydisciplinaire et polyprofessionnelle, "niche écologique" d'un CHU Parisien en France (Benoit, Cottin, & Moro 2017), et nourrie de quinze années de rencontres avec les adolescents souffrant de TCA et leurs familles ainsi que de notre implication dans le travail de réseau⁵. Si notre réflexion se veut générale elle ne saurait se départir, puisqu'elle s'y enracine, de l'appartenance disciplinaire originelle de l'auteure et de son cheminement personnel, intra et extra-institutionnel (Blanchet-Collet, Benoit, & Moro 2013). Dans la première partie de ce travail nous aborderons le contexte dans lequel s'est développé ce travail qui résulte d'une triple rencontre de l'épistémologie des TCA, de la sémantique et historique du concept de transdisciplinarité et d'une trajectoire personnelle et institutionnelle.

Dans une seconde partie nous aborderons les objectifs de ce travail et la méthodologie utilisée pour les atteindre, dans une troisième partie nous présenterons sous la forme de trois articles les résultats de notre recherche. Le premier article concerne une ébauche de modèle étiopathogénique intégratif, réalisé dans le cadre d'un groupe de recherche transdisciplinaire. Le second article est une overview transdisciplinaire des traitements médicamenteux dans l'AN réalisé à partir des méta-analyses et revues systématiques de la littérature.

⁵ Le réseau Régional TCA Francilien (www.reseautca-idf.org) et le réseau national Fédération Française Anorexie Boulimie (www.ffab.fr) sont des Associations Loi 1901, regroupant des professionnels de toutes disciplines et destinées à faire évoluer les soins et la recherche pour les patients souffrant de TCA. Ces associations travaillent en étroite collaboration avec la Fédération Nationale des Associations liées aux TCA destinée aux usagers et familles d'usagers (www.fna-tca.org).

Le troisième article est une position épistémologique qui suggère que le concept de transdisciplinarité est nécessaire pour modéliser le système complexe qu'est le "champ TCA".

La dernière partie constitue la discussion générale, qui permet de synthétiser nos différents travaux, construite autour de deux thèmes principaux qui concernent l'apport de la position transdisciplinaire dans le domaine de la compréhension et du soin, et par ailleurs les principes de la méthodologie transdisciplinaire dans le domaine de la recherche autour des TCA. La discussion se termine par des questions et quelques perspectives pour le soin et la recherche.

CONTEXTE

CONTEXTE

I. DEFINITIONS

a. LA TRANSDISCIPLINARITE

i. Définitions lexicales

Etymologiquement, le mot transdisciplinarité, est composé du préfixe latin “*trans*”: au-delà, passer d’ici à là, au travers, outre, et “*disciplina*”: formation, éducation, action d’apprendre.

Concernant les définitions lexicales, selon le Dictionnaire Larousse (2019)⁶, discipline peut être définie comme suit :

- “Branche de la connaissance pouvant donner matière à un enseignement ; matière
- Ensemble de lois, d’obligations qui régissent une collectivité et destinées à y faire régner l’ordre ; règlement
- Aptitude de quelqu'un à obéir à ces règles
- Obéissance, soumission aux règles que s'est données le groupe auquel on appartient
- Règles de conduite que l’on s’impose, maîtrise de soi, sens du devoir
- Sorte de fouet utilisé pour se flageller dans un but de mortification et de pénitence”.

Concernant les définitions sémantiques, pour Morin (1994) la discipline peut être définie comme “une catégorie organisationnelle au sein de la connaissance

⁶ Dictionnaire Larousse en ligne 2019 (<https://www.larousse.fr>).

scientifique ; elle y institue la division et la spécialisation du travail et elle répond à la diversité des domaines que recouvrent les sciences“.

Nissani (1995) définit une discipline comme tout domaine relativement autonome et isolé de l'expérience humaine qui possède sa propre communauté d'experts et un ensemble d'éléments distinctifs : objectifs communs, concepts, faits, compétences tacites, méthodologies, expériences personnelles, valeurs et jugements esthétiques (p122).

Concernant les définitions lexicales du mot transdisciplinarité, nous rapportons, par analogie avec les définitions Larousse (2019) des termes pluridisciplinarité ou interdisciplinarité, une définition de la transdisciplinarité comme “caractère de ce qui est transdisciplinaire“ ; en effet de façon étonnante, le terme transdisciplinarité est ignoré du Larousse.

Selon le Dictionnaire Larousse (2019), transdisciplinaire peut être défini comme suit : “qui dépasse les cloisonnements entre les disciplines“.

Selon le Dictionnaire Littré (2019)⁷, la transdisciplinarité peut être définie comme suit : “qualité des échanges et des relations entre les différentes disciplines du savoir“.

Selon le Centre National de Ressources Textuelles et Lexicales (CNRTL) (2019)⁸, la transdisciplinarité peut être définie comme suit : “une démarche scientifique qui dépasse les frontières d'une discipline“.

Concernant les définitions sémantiques du terme transdisciplinarité, nous rapportons les définitions proposées par différents auteurs, nommés les

⁷ Dictionnaire Littré en ligne 2019 (<https://www.littre.org>).

⁸ Centre National de Ressources Textuelles et Lexicales (CNRTL) 2019 : portail de ressources linguistiques informatisées (<https://www.cnrtl.fr>).

“passeurs prépondérants”, reliés à des références centrales sur la transdisciplinarité (Valade, 2013, p 80).

Selon Piaget (2012) :“(…) une étape supérieure qui serait “transdisciplinaire”, qui ne se contenterait pas d’atteindre des interactions ou réciprocitys entre recherches spécialisées, mais situerait ces liaisons à l’intérieur d’un système total sans frontières stables entre les disciplines” (p170).

Selon Morin (1994): “En ce qui concerne la transdisciplinarité, il s’agit souvent de schèmes cognitifs qui peuvent traverser les disciplines, parfois avec une virulence telle qu’elle les met en transe”.

Selon Nicolescu (1996): “La transdisciplinarité concerne, comme le préfixe latin « *trans* » l’indique, ce qui est à la fois entre les disciplines, à travers les différentes disciplines et au-delà de toute discipline. Sa finalité est la compréhension du monde présent, dont un des impératifs est l’unité de la connaissance” (p27).

Ces différentes visions permettent une compréhension que l’on pourrait qualifier de “transdisciplinaire” du concept de transdisciplinarité ; nous considérerons dans la suite de notre travail que la transdisciplinarité est un espace de savoir, de pensée et d’action généré par les interactions disciplinaires et se situant aux portes (entrouvertes) des disciplines.

ii. Origine et évolution conceptuelle

Le concept de transdisciplinarité a été introduit en 1970 par Jean Piaget, psychologue d’origine Suisse (1896-1980) à l’Université de Nice (France) à l’occasion d’une conférence co-organisée par le Ministère de l’Education et l’Organisation de Coopération et de Développement Economique (OCDE) (Piaget, 1972). Il n’est pas sans intérêt de rappeler que le titre initial de cette conférence comportait le terme “transdisciplinarité”, et que celui-ci a été modifié par les organisateurs au profit du mot “interdisciplinarité” jugé moins complexe et

moins inquiétant (Nicolescu, 2003). Eric Jantsch, astrophysicien australien et André Lichnerowicz, mathématicien français ont participé à cet événement. A l'occasion de la rencontre de l'OCDE, Piaget examinant les rapports mutuels existant entre les sciences formelles, les sciences de la nature et les sciences humaines, a distingué trois concepts que sont la pluridisciplinarité, l'interdisciplinarité et la transdisciplinarité qui illustrent non pas un ordre "hiérarchique" réductionniste entre les disciplines mais une hiérarchie dans les niveaux d'interaction et d'intégration qu'entretiennent ces disciplines, permettant de distinguer une typologie à trois niveaux:

- **Pluridisciplinaire** se caractérise par les phénomènes d'emprunt ou d'importation d'informations d'une science à l'autre, sans entraîner de modifications pour la discipline originale
- **Interdisciplinaire**, il y a, soit entre les disciplines, soit entre les secteurs "hétérogènes d'une même science", une réciprocité d'échanges "telle qu'il y ait au total enrichissement mutuel"
- **Au niveau transdisciplinaire**, les relations entre les disciplines se situeraient "à l'intérieur d'un système total sans frontières stables entre les disciplines " (Piaget, 1972, p169-170).

Selon Nicolescu (2011), la connaissance transdisciplinaire "*in Vivo*" se distinguerait de la connaissance disciplinaire "*in Vitro*" par différentes caractéristiques représentées par un système de valeurs (Tableau 1) (p97).

Connaissance disciplinaire	Connaissance transdisciplinaire
Monde externe-Objet	Correspondance entre le monde externe (objet) et le monde interne (sujet)
Savoir	Compréhension
Intelligence analytique	Nouveau type d'intelligence- équilibre entre le mental, les sentiments et le corps
Orienté vers le pouvoir et la possession	Orienté vers l'étonnement et le partage
Logique binaire	Logique du tiers inclus
Exclusion des valeurs (neutralité)	inclusion des valeurs (option humaniste)

TABLEAU 1 : Caractéristiques de la connaissance disciplinaire et transdisciplinaire (*adapté de Nicolescu, 2011, p98*).

Le concept de transdisciplinarité repose sur trois postulats que sont :

- **Les niveaux de Réalité** : terme proposé par Edmund HUSSERL (1859-1938), sont définis comme : “ ... deux niveaux de Réalité sont différents si, en passant de l’un à l’autre, il y a rupture des lois et rupture des concepts fondamentaux” (Nicolescu, 1996, p13)
- **La logique du Tiers Inclus** : terme proposé par Stéphane Lupasco (1900-1988), est définie comme : “une véritable logique, formalisable et formalisée, multivalente à trois valeurs (A, non-A et T) et non-contradictoire“ ; elle est “la logique“ de la complexité, transgression logique nécessaire servant à infléchir le tiers inclus (A, non-A, pas d’existence d’un terme T qui serait A et non-A) (Nicolescu, 1996, p18)
- **La Complexité** : terme crée par W. Ross Ashby (1903-1972), puis développé par Edgar Morin : “ la complexité est ce qui résiste aux méthodes réductionnistes qui ont fait le succès des sciences empiriques, elle est ce qui ne peut se réduire au simple, à un unique fait, principe ou cause“ (Lemoigne & Morin, 2007, p160).

Ces postulats permettent de définir trois axiomes qui constituent les fondements de la méthodologie transdisciplinaire :

- L'axiome ontologique : l'existence de différents niveaux de Réalité de l'Objet et de différents niveaux de Réalité du Sujet
- L'axiome logique : le passage d'un niveau de Réalité à un autre niveau de Réalité s'effectue par la logique du tiers inclus (s'opposant à la logique du tiers exclu)
- L'axiome épistémologique : la structure de l'ensemble des niveaux de Réalité apparaît, dans notre connaissance de la nature, de la société et de nous-mêmes, comme une structure complexe : chaque niveau est ce qu'il est parce que tous les autres niveaux existent à la fois (Nicolescu, 1996, p98).

Il existe bien d'autres concepts désignant diverses modalités d'interactions intra- ou interdisciplinaires, que nous regrouperons sous le terme générique de "polydisciplinaires". Ces différents concepts font, par ailleurs, l'objet de catégorisations (ou typologies) complexes (Thompson Klein, 2010) (Laflamme 2011) (Choi & Pak, 2006 ; Choi & Pak, 2007; Choi & Pak 2008). Ces échanges de savoir et de compétences entre disciplines, de niveaux et d'intensités variables, générant des retentissements favorables mais également des inconvénients sur la discipline, le sujet et/ou l'objet, ont été résumés dans le tableau ci-après (Tableau 2). Dans ce que certains auteurs ont nommé un "bourbier sémantique" (Leathard A, 1994, cité par Choi & Pak 2006, p352), la transdisciplinarité ne semble pas devoir être considérée comme le stade "ultime" d'un continuum entre ces différents concepts mais pourrait, dans une vision intégrative et unifiante, co-exister avec un ou plusieurs de ces concepts selon le contexte et la proximité épistémologique des champs disciplinaires impliqués (Letourneau, 2008).

TYPES d'INTERACTION DISCIPLINAIRE	CARACTERISTIQUES	AVANTAGES et INCONVENIENTS
Pluridisciplinarité	<p>Actions communes ou regards croisés de plusieurs disciplines juxtaposées sur un objet d'étude commun de manière plus ou moins coordonnée mais sans objectif commun</p> <p>Association de disciplines complémentaires</p> <p>La finalité reste inscrite dans la discipline</p>	<p>La démarche déborde le cadre disciplinaire</p> <p>Le degré d'intégration entre les disciplines se limite aux résultats de la recherche</p> <p>Pas de modification pour la discipline qui conserve ses spécificités (outils et vision)</p> <p>Première étape vers la recherche de complexité</p> <p>Possibles incompatibilité entre les acteurs de disciplines différentes</p> <p>L'objet d'étude est enrichi par le croisement de ces approches</p>
Interdisciplinarité	<p>Actions communes ou regards croisés et coordonnés de plusieurs disciplines sur un objet d'étude commun avec un objectif commun</p> <p>Objectif commun préalablement fixé par l'ensemble de l'équipe dans une approche globale</p> <p>Volonté d'échange et de partage d'outils et compétences entre disciplines ayant pour but une production commune ne permettant pas de discerner les apports spécifiques de chaque spécialité</p> <p>La finalité reste inscrite dans la</p>	<p>Interactions réciproques et rencontre des disciplines dont les frontières deviennent floues</p> <p>Niveau d'intégration constant mais d'intensité variable des outils/concepts spécifiques de chaque discipline et des problématiques réciproques des disciplines impliquées</p> <p>Echanges et enrichissement réciproques des disciplines dans l'espace « entre » les disciplines</p> <p>Dépendances réciproques entre les disciplines</p>

	discipline	Approche systémique de l'objet qui se trouve enrichi
Co-disciplinarité	Etude d'un objet par deux disciplines très proches formant une unité	Disciplines "indissociables" "imbriquées" "coopérantes"
Circum-disciplinarité	Diffusion du savoir en spirale des uns vers les autres	Transformation du savoir, de soi
Indisciplinarité	Posture s'affranchissant, sans les renier, des contraintes disciplinaires une fois les cultures disciplinaires intégrées	Liberté, créativité
Métadisciplinarité	Posture mentale intégrant les concepts essentiels des autres disciplines, associée à un ancrage puissant dans sa discipline d'origine Axiome commun à plusieurs disciplines	Dépasse les segmentations disciplinaires en les conservant Savoir global, méta-position pour le sujet Dépasse, englobe l'objet
Ego-interdisciplinarité	Acquisition par l'individu de notions ou concepts d'autres disciplines Nécessite une solide formation disciplinaire	Intelligence interdisciplinaire et créativité d'œuvres interdisciplinaires
Intradisciplinarité	Interrelations à l'intérieur d'un champ disciplinaire/entre les éléments d'une discipline	Enrichissement des sous disciplines Création de nouveaux outils
Cross-disciplinarité	Emprunt ponctuel par une discipline de concepts ou termes appartenant à une autre discipline	Modification partielle de certains concepts ou méthodes de sa discipline Risque « d'imposture intellectuelle »
Transdisciplinarité	Posture intellectuelle et nouvelle pensée qui se situe "entre, au-delà et au travers" des frontières des	Nécessité d'ancrages disciplinaires forts

disciplines réunies autour d'un objet commun	Favorise la dialectique disciplinaire
Le point de convergence des disciplines est l'objet unificateur justifiant la mise en commun d'outils	Haut niveau d'intégration des disciplines (compétences, connaissances, méthodes, apports épistémologiques) et disparition des frontières disciplinaires
Partage d'un modèle conceptuel commun qui intègre et transcende les perspectives spécifiques de chaque discipline/acteur scientifique ou non scientifique	Transversalité du savoir
Nouveau paradigme permettant une compréhension globale vers une théorie du "Tout"	Approche complexe et globale de l'objet : vision "totalisante et unifiante"
La finalité est la compréhension du monde présent	Participe à l'évolution/transformation de l'objet
	Participe à l'évolution/transformation des disciplines (concept unificateur et fécondant) et des compétences des acteurs (savoir, créativité)
	Risques identitaires professionnels, conflits interdisciplinaires, confusion des rôles

TABLEAU 2 : Classification des concepts polydisciplinaires désignant les relations et niveaux d'échange entre les disciplines- synthèse intégrative réalisée par l'auteur à partir des sources bibliographiques citées (Morin, 1994, Nicolescu, 1996, Choi & Pak, 2006, Thompson Klein, 2010, Laflamme, 2011, de la Trinonnière, 2014) .

Durant les années 1980, le développement de la "pensée complexe" incarnée par les travaux du sociologue et philosophe Edgar Morin (1921-) a largement contribué à l'avènement de la transdisciplinarité, dont le physicien théoricien Français d'origine Roumaine Basarab Nicolescu, deviendra le chef de file dans les années 1990. Basarab Nicolescu sera à l'origine de la création en Europe du

Centre International de Recherches Transdisciplinaires (CIRET)⁹ et cosignataire de la Charte de la transdisciplinarité élaborée à l'occasion du Premier Congrès Mondial de la Transdisciplinarité au Portugal en 1994 (Annexe II). En ce début de 21^{ème} siècle, plus d'une trentaine d'années après l'émergence du concept de transdisciplinarité, des projets de collaborations internationales transdisciplinaires en lien avec le CIRET se développent en Europe, ainsi qu'en Amérique avec des programmes de recherche-action-formation au Centre ARKOS au Mexique, et au Québec (Canada) (Galvani, 2008 ; Gonzales Garcia, 2014). Un programme d'intervention transdisciplinaire auprès des populations de jeunes Jamaïcains et leurs familles a été développé notamment face aux problèmes d'obésité dans un contexte de transculturalité (Ferguson, Fiese, Nelson, & Meeks Gardner 2019). Au niveau international, the Academy of Transdisciplinary Learning and Advances Studies (ATLAS)¹⁰, créée en 2000, regroupe des scientifiques et chercheurs de toutes disciplines autour de sujets complexes, comme les programmes d'éducation, visant à favoriser l'évolution de la pensée disciplinaire vers la pensée transdisciplinaire et les coopérations transnationales et transculturelles.

b. LES TROUBLES DES CONDUITES ALIMENTAIRES

i. Définitions et épidémiologie

Véritable problème de santé publique en Europe avec une prévalence estimée entre 350 000 et 900 000 d'individus en France (Godart, & Radon, 2017), les troubles des conduites alimentaires (TCA) concerneraient selon des études récentes 18 millions d'individus dans le monde (Hoek, 2006), (Keski-Rahkonen, & Mustelin, 2016). Les TCA sont des pathologies d'origine polyfactorielle, récemment qualifiées

⁹ Le Centre International de Recherches Transdisciplinaires (CIRET), association Loi 1901, a été fondé en 1987 (www.ciret-transdisciplinarity.org). Le CIRET vise à développer la recherche transdisciplinaire et favoriser le dialogue entre les professionnels et scientifiques de différents domaines. Les principales étapes de sa construction sont résumées dans l'annexe I.

¹⁰ The Academy of Transdisciplinary Learning and Advances Studies (ATLAS) est un organisme sans but lucratif qui fournit des services aux universités du monde entier.

de troubles “métabo-psychiatriques” (Anorexia Nervosa Genetics Initiative et al., 2019), survenant sur une trajectoire de vulnérabilité biopsychosociale répondant à des modèles intégratifs incorporant des données neuroscientifiques, génétiques et psychosociales (Treasure, & Schmidt, 2013). La prévalence de ces troubles complexes, dont les trois formes dominantes sont représentées par l’anorexie mentale, la boulimie et l’hyperphagie boulimique, concerne en Occident 7 à 10% des adolescents et jeunes adultes (Smink, et al. 2012 ; Roux, Chapelon, & Godart, 2013 ; Erskine, & Whiteford 2018). La période adolescente, par les modifications physiologiques/pubertaires induites, le processus de maturation psychique et de construction identitaire et les remaniements des interactions familiales et sociales, est une période de forte vulnérabilité, majorant le risque de survenue des TCA et d’autres troubles psychiques. Les TCA touchent néanmoins les individus de tout âge, concernent tous les genres (avec des sex ratio variables selon les catégories et les âges), et peuvent survenir dans tous les contextes socioculturels (Radjack, Guzman, Bouaziz, Revah, Moro, & Blanchet-Collet, 2013). Si la plupart des données épidémiologiques proviennent d’études Occidentales, des études récentes confirment l’émergence de ces pathologies dans les pays non-Occidentaux, notamment en Asie du Sud-Est, mais également en contexte transculturel pour les enfants de première ou deuxième génération issus de l’immigration (Nasser, 2006) (Vu-Augier de Montgrémier, Lachal, Blanchet-Collet, & Moro, 2016). Les TCA présentent une forte hétérogénéité et instabilité symptomatique au niveau intra et interindividuel (Fairburn, & Harrison, 2003 ; Monteleone, Di Genio, Monteleone, Di Filippo, & Maj, 2011) et différentes formes peuvent coexister ou se succéder chez un même individu. Ces pathologies sont associées à de multiples comorbidités somatiques, nutritionnelles et psychosociales qui peuvent être à la fois facteurs de vulnérabilité, facteurs favorisants et de maintien de ces troubles à haut risque de chronicité, de désinsertion socioprofessionnelle et de surmortalité (Steinhausen, & Weber, 2009 ; Arcelus, 2011). Si Pinel écrivit, en 1798, une nosographie philosophique, classification des maladies mentales où sont cités dans la catégorie “Névrose du Conduit Alimentaire les perversions de l’appétit et de la digestion”, l’entrée des TCA dans les classifications nosographiques au cours de la deuxième

partie du vingtième siècle avec les classifications de la CIM-1 (OMS) et du DSM-I (APA) en 1948, correspond à l'avènement de la conception psychogénique des TCA. Les TCA, sont actuellement définis selon une approche catégorielle synchronique par les systèmes nosographiques actuels de la CIM-10 et du DSM-5 (Tableau 3), influencée par les travaux de Hilde Bruch (1904-1984) sur l'image du corps (Bruch, 1962). Ces classifications dites "athéoriques" visant à définir des groupes homogènes de malades sont complétées par d'autres approches nosographiques comme le Psycho Dynamic Manual (Speranza, et al., 2017) intégrant l'expérience subjective du patient ou l'approche transdiagnostique (Wade, Bergin, Martin, Gillespie, & Fairburn, 2006) qui offre une vision diachronique du trouble reflétant l'hétérogénéité phénotypique de ces troubles polymorphes.

CIM 10	DSM 5
Pica	Pica
Trouble de l'alimentation du nourrisson ou de l'enfant	Mérycisme <i>Rumination Disorder</i>
	Restriction ou évitement de l'ingestion d'aliments <i>Avoidant Restrictive Food Intake Disorder (ARFID)</i>
Anorexie mentale Anorexie mentale + boulimie Anorexie mentale atypique	Anorexie mentale type restrictif ou hyperphagique/ purgatif <i>Anorexia Nervosa restricting or binge eating/purging type</i>
Boulimie nerveuse Boulimie nerveuse atypique	Boulimie <i>Bulimia Nervosa</i>
Hyperphagie associée à d'autres perturbations psychologiques	Hyperphagie boulimique <i>Binge Eating Disorder</i>
Autre trouble de l'alimentation Autre trouble de l'alimentation non spécifié Vomissements associés à d'autres perturbations psychologiques	Autre trouble de l'alimentation ou de l'ingestion d'aliments, spécifié <i>Other Specified Feeding or Eating Disorder (OSFED)</i>
	Autre trouble de l'alimentation ou de l'ingestion d'aliments, non spécifié <i>Unspecified Feeding or Eating Disorder (UFED)</i>

TABLEAU 3 : Nosographies catégorielles des troubles des conduites alimentaires : Classification Internationale des Maladies (CIM-10) de l'OMS et Diagnostic and Statistic Manual (DSM 5) de l'APA (adapté par l'auteur à partir du DSM 5 traduit).

ii. Épistémologie des figures anorexiques et des approches collectives

L'épistémologie des approches collectives des TCA a évolué parallèlement aux modèles explicatifs de ces troubles, et apparaît étroitement et historiquement liée à celle des "figures anorexiques", autour desquelles se sont construits les différentes approches au fil du temps. Le choix du mot "figure", terme non "genré", renvoie à une filiation où les sujets, le plus souvent (mais non exclusivement) féminins, engagés dans des conduites alimentaires que l'on pourrait qualifier de déviantes en référence à la transgression d'une norme sociale et aux valeurs morales admises et attendues dans un contexte socioculturel et une époque donnés s'inscrivent dans une filiation venant entre autre questionner la libre disposition de soi. L'histoire de l'humanité est ainsi jalonnée, D'Antigone aux "Indomptables" (Raimbault, & Éliacheff, 1996), jusqu'aux figures plus contemporaines littéraires de "l'écriture anorexique" (Meuret, 2006) de "figures anorexiques", empruntant au fil de l'histoire, les valeurs à disposition, faisant tour à tour référence aux valeurs religieuses, mystiques ou sociétales de l'époque (Figure 1). Ainsi, l'épistémologie des TCA débute bien avant l'ère dite "médicale" avec les premières descriptions de conduites de restriction alimentaire, supposément associées à des pathologies organiques, par les médecins Grecs (Hippocrate de Cos 460-377 av. J.-C.) ou des orgies alimentaires avec vomissements provoqués dans l'Empire Romain décrites par Galien de Pergame (Claude Galien, 130-210 ap. J.-C.) ou l'Antigone de Sophocle (Sophocle, 495-406 av. J.-C.). Après les pré-figures anorexiques de l'Antiquité, la "généalogie" des TCA se poursuit au Moyen Âge avec la "mystique affective féminine doloriste" (Maître, 2000). La sécularisation de l'anorexie, étape essentielle dans l'histoire des TCA, permet de traverser le champ religieux et de pénétrer le champ laïque sociétal puis médical à partir du 19^{ème} siècle.

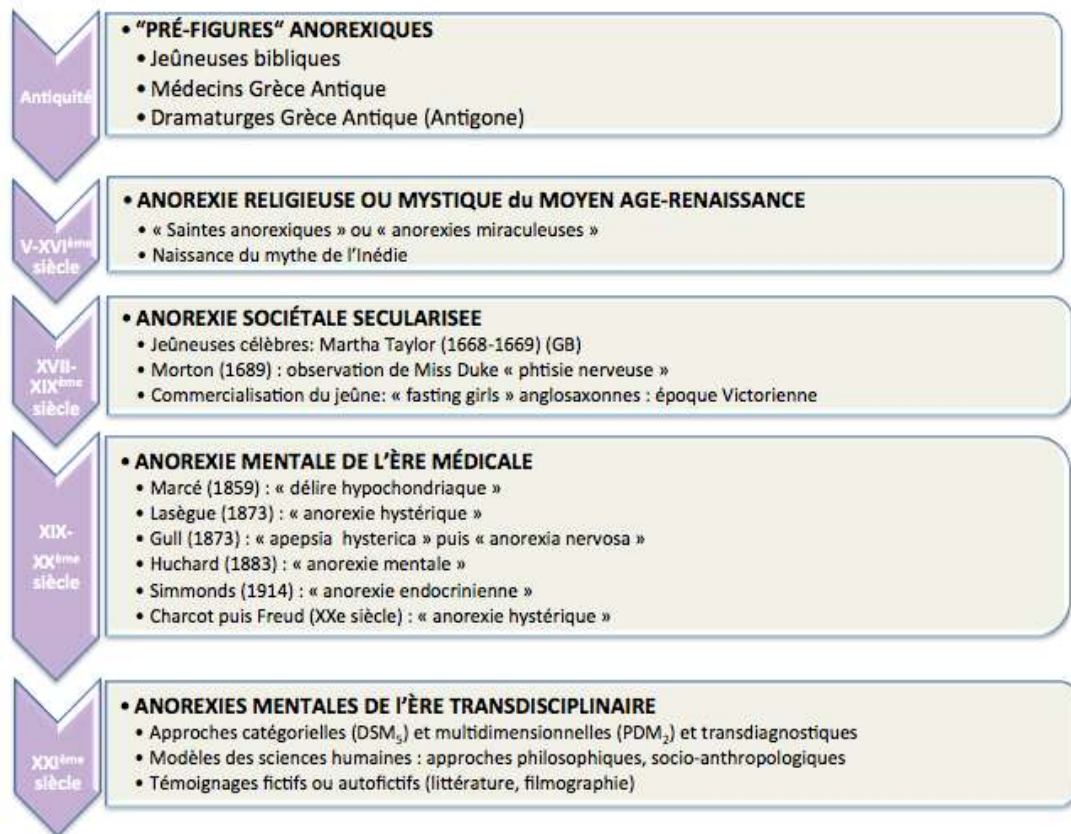


FIGURE 1: Épistémologie des figures anorexiques: généalogie de l'Anorexie Mentale au fil des siècles: des pré-figures anorexiques de l'Antiquité à l'Anorexie mentale de l'ère transdisciplinaire au XXI^{ème} siècle (Communication personnelle de l'auteur-16^{ème} congrès de l'European Council on Eating Disorders-Sept. 2019).

A partir de l'ère médicale, les approches collectives se construisent progressivement, autour des jeunes femmes souffrant d'anorexie, qui devient figure emblématique des TCA. La conception initiale individuelle de l'anorexie mentale comme symptôme psychiatrique par les pères fondateurs que sont Louis Victor Marcé (1828-1864), Ernest-Charles Lasègue (1816-1883) et William Withey Gull (1816-1890), a été à l'origine d'une systématisation du traitement par les aliénistes du 19^{ème} siècle, Jean-Martin Charcot (1825-1893) et Jules Dejerine (1849-1917), avec isolement (supposé) thérapeutique, dans un environnement carcéral et coercitif (Brusset, 1977). Cette position mono disciplinaire dogmatique qui fait partie de la mémoire collective du monde

médical occidental a incontestablement influencé l'évolution et la représentation des soins dans le champ des TCA. L'épistémologie des approches collectives est également marquée par la confrontation précoce entre partisans de la théorie psychologique (psychogénétique) et de la théorie physiologique (organogénétique), au début du 20^{ème} siècle, avec la proposition par un pathologiste Allemand, Morris Simmonds (1914) d'une cause endocrinienne à l'anorexie mentale et les dérives de l'opothérapie ultérieurement rapportées (Decourt, 1951). Si la théorie endocrinienne comme modèle causal s'efface en quelques décennies, la découverte des repercussions organiques de la dénutrition au travers des tableaux de *pitutary-cachexia* reste, même sur un malentendu, une étape marquante de la rencontre des psychiatres et des médecins organicistes autour des intrications *soma-psyché*. Renforcé par l'effacement des théories physiologiques, on assiste au milieu du 20^{ème} siècle, à la réémergence des théories psychogéniques mais l'intégration de dimensions organiques et environnementales demeure acquise (Bruch, 1962 ; Bruch, 1979 ; Brusset, 2008). Le symposium de Göttinguen (1965) entérine la conception psychopathologique de l'AM, et le congrès de Toronto (1981) marque l'avènement du modèle biopsychosocial proposé par Garfinkel (Raimbault, & Éliacheff, 1996, p51). Si le modèle psychanalytique inspiré des théories Freudiennes, reste le modèle prévalent jusqu'aux années 1980 (Jeammet, 1985 ; Corcos, 2005 ; Corcos, 2010) on assiste à la fin du 20^{ème} siècle, à une diversification accélérée des approches thérapeutiques. Les programmes de soins institutionnels "inpatient treatment" et les hospitalisations programmées avec "contrat-séparation" se développent dans des unités de soins psychiatriques spécialisées (Godart, Perdereau, Galès, Agman, Deborde, & Jeammet, 2005) parallèlement à l'introduction des soins psychothérapeutiques ambulatoires individuels "outpatient psychosocial treatment" et d'approches de type systémique (Vincent, 2009).

Les figures anorexiques du 21^{ème} siècle, comme leurs aînées, ont enrichi et participent à élargir le champ épistémologique des TCA, par leurs témoignages, notamment au travers de la littérature : "Anorexie et écriture n'ont pas

seulement essayé ensemble mais ont grandi ensemble“ (Groulez, 2006). Les romans, récits autobiographiques ou philosophiques des “figures littéraires anorexiques“ telles que Valérie Valère (Valère, 1978), Michela Marzano (Marzano, 2012), Delphine de Vigan (De Vigan, 2001), Sheila Mc Leod, (Mc Leod, 1992) Ysabelle Lacamp (Lacamp, 1999) ou Geneviève Brissac (Brissac, 1994) ou hommages et témoignages de leurs proches, ou les écrits où le TCA est “suggéré faute d’être nommé“ (Joseph Kafka, les sœurs Brontë, Emily Dickinson, Virginia Woolf, Amélie Nothomb) (Meuret, 2006) sont autant de témoignages de ces figures anorexiques contemporaines. Plus récemment, la filmographie, notamment Québécoise, vient enrichir le champ des témoignages écrits : “La peau et les os“ (1988) de Johanne Prigent, suivi de “La peau et les os Après“ (2006), “Black Swan“ de Darren Aronofsky (2010), “To the bone“ de Marty Noxon (2017) et plus récemment un documentaire allemand particulièrement saisissant en plusieurs parties et au long cours, qui vient questionner l’éthique du soin “Emma Wants to live“ de Jessica Villerius (2017). Nous ajouterons les témoignages portés par les “blogs“ actuels, sujet à controverse, diffusant pour certains un discours qui prône le TCA comme un mode de vie et en font l’apologie, et à l’inverse ayant pour d’autres une fonction d’étayage luttant contre l’isolement et l’engagement dans le symptôme (Casilli, 2016).

Au 21^{ème} siècle, la conception globale du soin fait écho à la conception polyfactorielle des ces troubles complexes et à la pluralité des modèles explicatifs proposés. Les approches intégratives associent des stratégies thérapeutiques individualisées (Vincent, 2009 ; Vanderlinden, 2010) et des approches familiales “family-based approach“ (Lock & Fitzpatrick, 2009; Godart, et al., 2012 ; Cook-Darzens, 2014 ; Eisler, et al., 2016). Le cadre et les modalités d’hospitalisations ont considérablement évolué (Blanchet-Collet, 2014) et les soins psychothérapeutiques se sont enrichis des approches psychodynamiques (Jeammet, 1993), cognitivo-comportementales (Fairburn, et al., 2009), addictologique (O’Hara, Campbell, & Schmidt, 2015) ou transculturelle (Lee, 1996 ; Soh, Surgenor, Touyz, & Walter, 2006). Les programmes de soins actuels associent des approches coordonnées intégrant le soin psychiatrique,

psychosocial, somatique et nutritionnel dans des environnements thérapeutiques polyprofessionnels et polydisciplinaires, prenant en charge le patient et son entourage tels que recommandés par les guidelines internationaux (Haute Autorité de Santé, 2010 ; Haute Autorité de Santé, 2019 ; American Psychiatric Association, 2006 ; National Institute for Health and Care Excellence, 2017), (Figure 2).

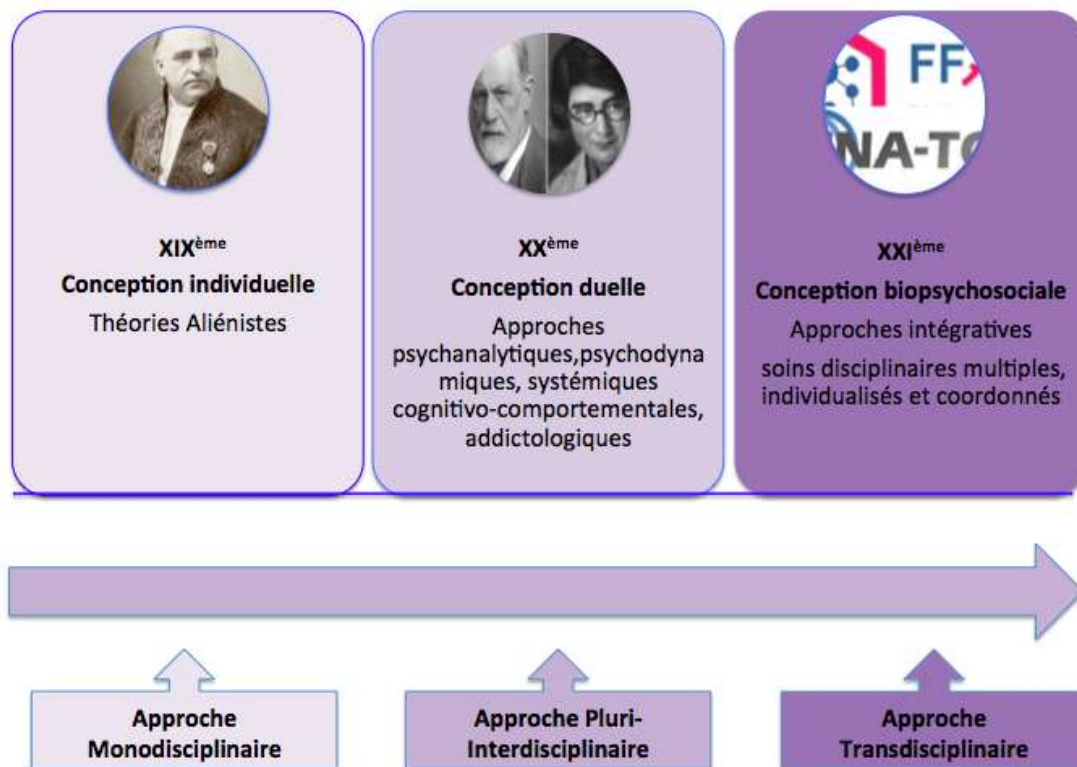


FIGURE 2 : Épistémologie des approches collectives des TCA: changement paradigmatique d'une conception individuelle du trouble associée à une approche monodisciplinaire dogmatique à une conception biopsychosociale avec approche transdisciplinaire. (Communication personnelle de l'auteure-16^{ème} congrès de l'European Council on Eating Disorders-(ECED)-Sept. 2019)

c. MAISON des ADOLESCENTS-MAISON de SOLENN

i. Historique des Maisons des Adolescents

Les Maisons des Adolescents (MDA), dont la première fut créée en 1999 au Havre sont nées d'une commande Ministérielle faisant état d'une carence majeure de structures adaptées pour la tranche d'âge 12-25 ans (Fuseau, 2009), d'une indisponibilité et d'une insuffisance des moyens pour accueillir l'adolescent, son processus développemental, son mal-être et ses pathologies (Rufo, & Joyeux, 2004). Après la Conférence des Familles en 2003, ce nouveau concept de "Maison des Adolescents" s'est développé dans les différentes régions, donnant naissance à plus d'une centaine de MDA déployées sur l'ensemble du territoire national. Ces structures, partageant une triple mission de prévention, d'éducation et de soins, présentent des fonctionnements et des modalités de financement extrêmement hétérogènes et sont déferés par l'ANMDA¹¹ (Moro, 2012). Ces lieux, qui se doivent d'être facilement identifiables et accessibles aux adolescents, à leurs familles et aux professionnels, ont développé une éthique généraliste et spécifique de l'accueil (Perret et al., 2012) et répondent depuis les années 2000 à des besoins spécifiques pour cette population qui s'articule avec les dispositifs préexistants. Parmi la cinquantaine de MDA existant en France, la Maison des Adolescents de Paris Sud- Maison de Solenn, vient renforcer l'offre de soins globale mais a également développé une expertise pour des problématiques spécifiques comme les TCA, les refus scolaires anxieux, les souffrances psychiques associées à des pathologies somatiques chroniques sévères (diabète, obésité, maladies rares), l'adoption internationale ou les problématiques transculturelles (Benoit, et al., 2018).

¹¹ Association Nationale des Maisons des Adolescents (ANMDA) (www.anmda.fr). L'ANMDA a été fondée en 2003 et fédère l'ensemble des Maisons des Adolescents déployées sur le territoire.

ii. La Maison de Solenn

La Maison des Adolescents de Paris Sud-Maison de Solenn, ouverte en Décembre 2004, est un service hospitalo-universitaire¹² rassemblant dans une même unité de temps et de lieu une équipe pluridisciplinaire constituée de médecins somaticiens, de psychiatres et de pédopsychiatres, de psychologues, diététiciens, professionnels para-médicaux, d'autres intervenants du milieu socio-éducatif et d'enseignants. L'un des défis majeurs de cette pratique institutionnelle, au-delà de la création d'une offre de soins diversifiée et individualisée dans un environnement thérapeutique innovant, réside dans la mise en commun des compétences disciplinaires et professionnelles variées nécessitant la création et le partage d'une culture médicale commune entre les différents acteurs impliqués (Benoit, Smadja, Benyamin, & Moro, 2011). Un autre défi conséquent consiste à accueillir une grande mixité de pathologies somatiques, nutritionnelles et psychiatriques et à faire cohabiter la souffrance adolescente au-delà de l'extrême hétérogénéité symptomatique. La Maison de Solenn a développé entre autres domaines d'expertise, une offre de soins spécifique pour les adolescents souffrant de TCA, leurs familles et construit des liens et collaborations avec de nombreux partenaires dans le cadre de l'ANMDA, du réseau TCA Francilien¹³ et de la FFAB¹⁴. La Maison de Solenn a ainsi développé une filière de soins spécialisée qui offre aux patients souffrant de TCA une approche pluridisciplinaire, individualisée et coordonnée intra-institutionnelle s'articulant avec les soins ambulatoires extra-institutionnels, les différentes structures ambulatoires existantes et les partenaires du Réseau TCA Francilien. Le parcours de soin intra-institutionnel de l'adolescent souffrant de TCA, se déroulant le plus souvent sur de nombreuses années en raison de la sévérité et du caractère chronique et récidivant de ses troubles, s'articule autour

¹² Service de l'Hôpital Cochin-APHP-Université de Paris-Dirigée par le Pr Marcel Rufo de 2004 à 2007 et depuis 2008 par le Pr Marie Rose Moro. www.maisondesolenn.fr- Soutenue par la Fondation Hôpitaux de Paris-Hôpitaux de France

¹³ Réseau des Troubles des Conduites Alimentaires Francilien (www.reseautca-idf.org).

¹⁴ Fédération Française Anorexie Boulimie (FFAB) (<https://www.ffab.fr>).

de différentes unités fonctionnelles interactives qui sont : un espace d'accueil sans rendez-vous (espace santé), des consultations pluridisciplinaires incluant une offre de psychothérapie individuelle, mono- et multifamiliale, un hôpital de jour spécialisé pour adolescents souffrant d'anorexie mentale, une unité d'hospitalisation temps plein polydisciplinaire, polyprofessionnelle et polypathologies intégrant des soins pédopsychiatriques, psychosociaux et éducatifs, somatiques et nutritionnels (Blanchet-Collet, et al., 2013). Ainsi différents niveaux de réalité se sont d'emblée superposés dans un environnement transdisciplinaire qui "structurellement" présentait de multiples espaces différenciés, que l'on pourrait nommer "espaces transitionnels" (Winicott, 2018), permettant un accueil spécifique et singulier à chaque étape de la trajectoire individuelle et institutionnelle du patient. Différentes médiations à type d'art thérapie, d'approche corporelle, de réadaptation au sport, et autres ateliers culturels viennent diversifier et renforcer les soins en offrant un espace de parole, d'expression et créativité favorable à la rencontre avec l'adolescent. D'autres programmes de soins transdisciplinaires spécialisés comme les programmes d'Éducation Thérapeutique pour le Patient (ETP) pour les patients souffrant d'anorexie mentale en hôpital de jour, ou souffrant de boulimie en consultation, ou encore un programme transition adolescent-adulte (Blanchet-Collet, Lefevre, & Moro, 2017 ; Carles, Lachal, Moro, & Blanchet, 2019) ont été développés au cours des dernières années. Des groupes de paroles pour les parents (Giraud, & Moro, 2014) ou pour les fratries de patients souffrant de TCA (Persico, Grandclerc, Giraud, Moro, & Blanchet, 2019) viennent renforcer la prise en charge familiale globale. La réflexion autour de cette approche originale et inédite proposée à la Maison de Solenn, construite pas à pas, durant de longues années, pour les patients adolescents souffrant de TCA et leurs familles, dont les trajectoires de soins prolongées s'associent souvent à un vécu douloureux et chaotique, est à l'origine de ce travail de thèse.

II. GENESE

a. LE PARCOURS de L'AUTEURE

Ce travail de thèse est né de questionnements issus d'une triple rencontre qui inclut le parcours de l'auteure que l'on pourrait qualifier d'initiatique, le champ institutionnel des TCA, et le concept nomade de transdisciplinarité. Investie dès la première heure dans l'élaboration du projet institutionnel, et depuis quinze ans auprès des patients souffrant de TCA et de leurs familles, cette réflexion s'est imposée plus qu'elle n'a été consciemment choisie, probablement associée à notre position située "entre, au-delà, et au travers" des limites disciplinaires, et traversée par des apports épistémologiques, et l'intégration de concepts issus des multiples disciplines et acteurs croisés dans cet environnement fertile.

En introduction à la genèse de ce projet, nous rapportons la trajectoire personnelle de l'auteure dont la formation initiale académique est une formation médicale spécialisée d'endocrinologue-nutritionniste¹⁵ que l'on peut qualifier de "classique", dans un environnement hospitalo-universitaire parisien. Cette formation disciplinaire initiale, fondée sur un enseignement théorique spécialisé et sur une formation pratique (*praxis*) diversifiée dans des services d'endocrinologie et de diabétologie mais également dans des services de "sur-spécialités" comme la nutrition ou l'endocrinologie de la reproduction, s'est enrichie à l'occasion d'un post-internat dans un service d'endocrinologie parisien¹⁶ dont le domaine d'expertise dans le soin et la recherche dans le champ des pathologies surrénaliennes et hypophysaires bénéficiait d'une reconnaissance internationale. Les patients souffrant de ces pathologies endocriniennes chroniques présentent des comorbidités psychiatriques fréquentes induites par les modifications hormonales, les lésions tumorales ou séquellaires de traitements chirurgicaux ou radiothérapeutiques hypothalamo-hypophysaires nécessitaient fréquemment le recours à des soins psychiques,

¹⁵ DES en "endocrinologie-diabétologie-métabolisme" et DESC de Nutrition.

¹⁶ Service d'Endocrinologie des Pr Jean-Pierre Luton-Pr Xavier Bertagna-Hôpital Cochin-APHP-Paris.

voire l'intervention de la psychiatre attachée à la structure (ce qui il y a 30 ans était très exceptionnel dans les services de médecine somatique). Ce service avait également précocement développé sous l'impulsion de son chef de service, une appétence et une compétence particulière autour deux thématiques singulières qui étaient les dysphories de genre (ce service est encore actuellement en charge de l'évaluation endocrinienne des patients engagés dans une transition transgenre) et les troubles des conduites alimentaires (TCA). La prise en charge de patients adultes souffrant de TCA en service d'endocrinologie dans les années 1990 était encore commune, lointaine tradition héritée de la théorie "endocrinienne" de l'anorexie du début du 20^{ème} siècle. Si le modèle causal endocrinien s'est rapidement effacé au profit des théories psychogéniques, la découverte des repercussions organiques de la dénutrition au travers des tableaux cliniques de "pseudo-panhypopituitarisme" est restée, même sur un malentendu, une étape marquante de la rencontre des psychiatres et des médecins organicistes autour des intrications *soma-psyché*. La trajectoire de l'auteure est également marquée par deux étapes décisives la première ayant initié sa formation de spécialité dans un service de nutrition pionnier¹⁷ dans l'approche globale des patients souffrant d'obésité morbide, où médecins nutritionnistes, diététiciennes, psychologues et psychiatres partageaient une culture médicale commune. La seconde étape, décisive, fut sa formation de sur-spécialisation en Médecine de l'Adolescent (Fellowship) effectuée dans un service d'un hôpital pédiatrique à Montréal (Canada), service pionnier¹⁸ en Amérique du Nord ayant développé la Médecine de l'Adolescent, sous l'impulsion de la pédiatre Iris LITT, dans les années 1970, et construit des programmes de soins interdisciplinaires pour les patients souffrant de TCA (Wilkins, 2012).

¹⁷ Service de Nutrition des Prs Bernard Guy-Grand et Arnaud Basdevant-Hôpital Hôtel-Dieu-APHP-Paris

¹⁸ Service de médecine de l'Adolescent du Pr Jean Wilkins-Hôpital Sainte Justine-Montréal-Québec-Canada

Cette trajectoire initiatique est faite d'étapes successives et de "couches" de vécu subjectif au contact d'une médecine holistique et humaniste qui ont participé à la construction de connaissances théoriques spécialisés (*épistémè*), mais également d'un savoir (*gnose*), de cognitions, d'émotions, et d'éléments identitaires (Vermersch, 2006). C'est donc à l'issue de ce long chemin, que le vécu subjectif et l'expérience qui en résulte ont permis à l'auteure d'acquérir, "entre, à travers et au-delà" les frontières disciplinaires une ouverture à la transdisciplinarité qui a favorisé la rencontre avec le projet de la Maison de Solenn et plus tardivement avec l'élaboration du travail présenté. Nous souhaitons relater un épisode illustrant les difficultés à se représenter la rencontre des disciplines et des disciples qui en sont issus. L'anecdote se déroule, avant l'ouverture de la Maison de Solenn, dans le bureau du chef de service d'endocrinologie chargé de recruter un(e) endocrinologue hospitalier(e) qui "pourrait s'engager auprès des patients adolescents souffrant de TCA". Ses paroles furent les suivantes : "trouver un endocrinologue qui accepte de travailler avec des patients souffrant de TCA n'est pas simple, mais qui de surcroît accepte de travailler avec des psychiatres relève de l'impossible! vous ne devriez pas avoir beaucoup de concurrence"...le défi était lancé...nous étions en 1999...

b. LE CHAMP INSTITUTIONNEL des TCA

Force est de constater vingt années plus tard, que l'improbable rencontre disciplinaire s'est muée en un concept fertile mis au service des adolescents et de leur entourage. Comme nous l'avons précédemment décrit la "MDA-Maison de Solenn", si elle répond au cahier des charges commun à toutes les MDA (Huerre, 2011), a de facto était mandatée pour développer une approche originale et créative pour les adolescents souffrant de TCA. Les principales exigences étant de faire avec l'existant (ce qui revenait à développer les collaborations et le travail de réseau), faire autrement (afin de diversifier l'offre de soins spécifique) et surtout faire avec l'adolescent (sa subjectivité, sa temporalité, ses spécificités) et son entourage familial et socioculturel. Les approches développées pour les patients souffrant de TCA, prenant en compte ces différentes injonctions, ont abouti à construire un accueil spécifique proposant une évaluation et une orientation adaptées et un cadre de soin original permettant d'accompagner le patient et sa famille sur la longue trajectoire de la pathologie TCA et reconduire le sujet sur le chemin de son adolescence (Blanchet-Collet, et al., 2013). Un dispositif de soin institutionnel complexe s'est ainsi développé pour les adolescents souffrant de TCA dont nous citerons les principales caractéristiques:

- une approche polyprofessionnelle et polydisciplinaire
- un dispositif d'accueil spécifique protocolisé
- un parcours de soin institutionnel coordonné
- un projet de soin spécifique et individualisé
- une approche familiale incluant parents et fratrie
- une approche transculturelle
- une offre de soins ambulatoires simples ou renforcés (HDJ)
- une hospitalisation contractualisée sans séparation
- des modalités d'hospitalisation diversifiées (hospitalisation temps plein, séquentiel de semaine, séquentiel de week-end)
- un travail en réseau

Cette filière de soin spécialisée s'est ainsi construite au sein de la Maison de Solenn, autour du patient souffrant de TCA qui a convoqué autour de lui les professionnels et disciplines et autres acteurs qui participent à la mise en place et au maintien du cadre de soins. Différentes collaborations avec des partenaires extra-institutionnels et les réseaux régional et national se sont développés. Ce système composé d'un ensemble de sous-systèmes rassemblés autour d'un objet commun, partageant des connaissances, un savoir et une épistémologie commune constituent ce que nous nommerons dans la suite de notre travail le "champ TCA". Les différents acteurs et sous-systèmes impliqués dans le champ TCA sont présentés dans la suite de notre travail (Figure 3).

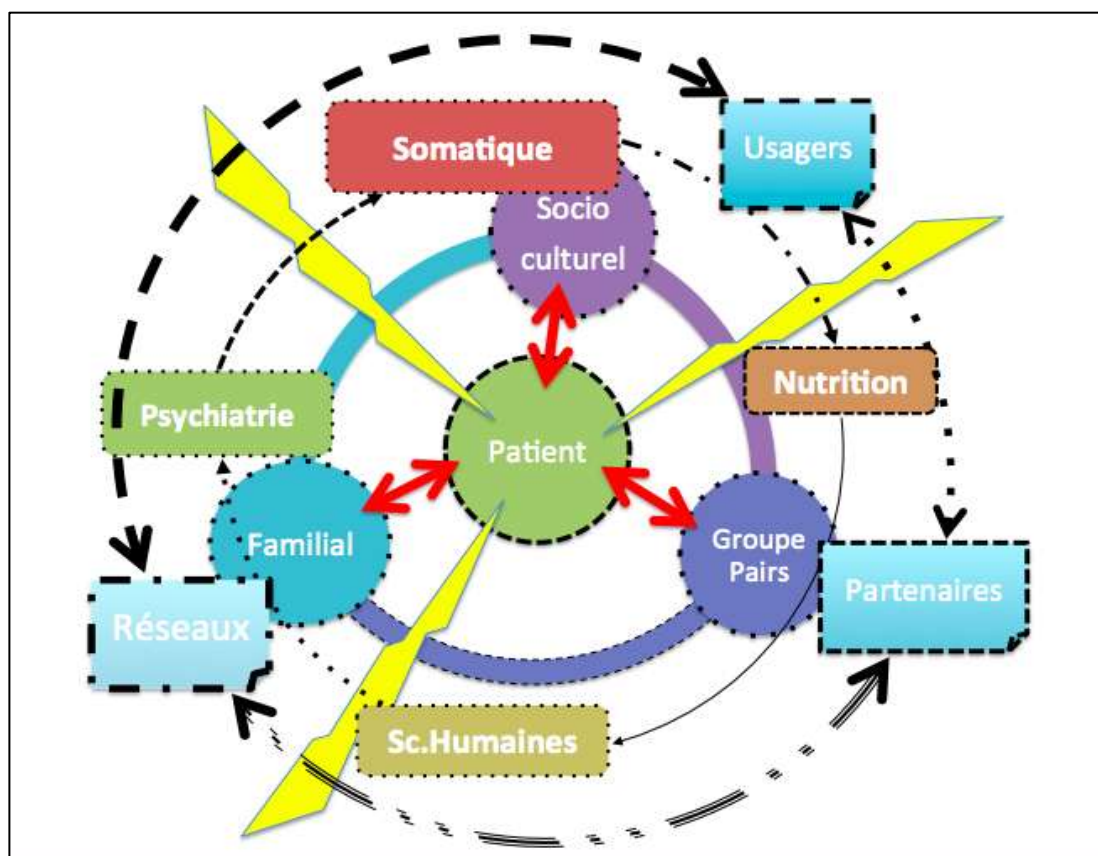


FIGURE 3 : Représentation schématique du champ institutionnel des TCA : un système complexe constitué de plusieurs sous-systèmes convoqués par l'objet TCA et soumis à des interactions multiples se déroulant "entre, au-delà ou au travers" des frontières des disciplines et de l'objet. Chaque sous-système (environnemental, soin, autres protagonistes) est constitué d'acteurs soumis à des interactions réciproques directes ou indirectes avec l'objet. L'espace est traversé par des savoirs, théories, outils partagés entre les différentes disciplines. Le système est parcouru par des courants (flèches éclairs) correspondant aux contributions épistémologiques provenant des différentes disciplines, mais également de l'épistémologie des figures anorexiques et des approches collectives qui participent respectivement à la philosophie et à l'éthique du soin et au cadre thérapeutique actuel.

i. L'adolescent souffrant de TCA

L'adolescent souffrant de TCA bénéficie de l'accueil et du cadre de soins général offert à tous les adolescents en souffrance circulant ou séjournant, pour des durées variables, dans l'environnement institutionnel. Néanmoins, si les spécificités de "l'objet TCA", ont su rassembler, favoriser et entretenir la dialectique disciplinaire, elles savent également favoriser les clivages interdisciplinaires et interprofessionnels. Ces patients présentent un haut niveau de complexité inhérent à l'hétérogénéité et la forte instabilité symptomatique, à la diversité des comorbidités associées, mais également lié à l'incertitude pronostique symptomatique, psychiatrique et globale. La pathologie TCA est une maladie cumulant tous les paradoxes : "Anorexia is baffling, paradoxical and contradictory" (Mc Leod, 1982 ; Jeammet, 2010). Les TCA sont à haut risque de chronicité mais curables, l'anorexie mentale est à la fois maladie de la dépendance et quête d'autonomie, à la fois rébellion et élitisme normatif revendiqué, présente différents niveaux de réalité nécessitant des soins adaptés. L'équipe soignante polyprofessionnelle et polydisciplinaire engagée auprès de ces patients, et particulièrement face aux patients souffrant d'anorexie mentale, doit faire face au déni, à l'ambivalence face aux propositions thérapeutiques et au processus de guérison, voire à l'hostilité et au refus de soins. La prise en charge disciplinaire conjointe et la rencontre des multiples savoirs disciplinaires et des différentes contributions épistémologiques permettent de mieux accueillir la complexité des symptômes somatiques et psychiatriques mais également de signes cognitifs et comportementaux et des mouvements d'agressivité régulièrement projetés sur l'équipe soignante (Darmon, 2003). Le sujet souffrant de TCA est engagé dans des relations inter-subjectives complexes avec les autres acteurs du champ TCA. Tous les professionnels de ce champ, somaticiens, diététiciens, soignants ou autres acteurs du système de soins (socio-éducateurs, enseignants, intervenants dans les médiations) sont, comme les psychologues et psychiatres, confrontés à des mouvements contre-transférentiels défensifs. L'insuffisance de formation des professionnels souligne et légitime la nécessité

du travail en commun pour reconnaître ces mouvements contre-transférentiels individuels et institutionnels et les élaborer collectivement. Les interactions complexes se situent également au niveau systémique entre le “sujet souffrant de TCA” et son environnement au sens large : environnement familial et socioculturel et le groupe de pairs. La subjectivité du patient interagit, durant les soins ambulatoires et en hospitalisations avec les subjectivités des autres adolescents ; dans le cadre des soins apportés aux patients souffrant de TCA, si l'étayage fourni par le groupe de pairs est indéniable, les enjeux relationnels et l'assimilation aux patients encore engagés dans le processus anorexique peuvent constituer un frein au “désengagement anorexique” (Darmon, 2003) et constituer un obstacle à la guérison. Enfin la dimension systémique du symptôme et les souffrances intra-familiales pré-existantes et/ou favorisées par la maladie chronique et la tyrannie du symptôme exercée sur l'entourage familiale et notamment la fratrie justifient le renforcement des approches “family-based” (Lock, & Fitzpatrick, 2017) incluant la mise en place d'espace de paroles intra-institutionnels destinées aux parents (Giraud, & Moro, 2014) mais également aux fratries (Persico, et al., 2019).

ii. Le système de soins

Au cours de son parcours institutionnel se déroulant souvent sur plusieurs années, l'adolescent souffrant de TCA et sa famille se retrouvent au centre d'un système de soins complexe. Le patient au cours de sa trajectoire investit successivement, plusieurs unités de lieux, alternant suivis ambulatoires, hôpital de jour, hospitalisations, où se construisent et s'articulent plusieurs projets successifs visant des objectifs de soins variés et évolutifs dans le temps adaptés aux besoins et aux compétences du patient. La complexité de ce système de soin résulte de la rencontre de ces différents niveaux de réalité mais également de la multitude des relations inter subjectives générées, au fil de ce parcours, entre le patient et les différents intervenants médicaux et non médicaux rencontrés lors de ces étapes de soin. Dans ce système, les disciplines médicales (médecine

somatique, nutrition, psychiatrie) et des sciences humaines (psychologie, sciences éducatives et sociales) croisent leurs savoirs, leurs compétences, leur langage, et leurs outils de soin. Certaines questions concernant la philosophie du soin et les objectifs à atteindre (objectifs de poids, guérison), ou les modalités de renutrition, les indications de traitements médicamenteux psychotropes (neuroleptiques, régulateurs de l'humeur) ou hormonaux (retards staturaux, pubertaires), ou certaines questions éthiques comme les refus de soins sont susceptibles de générer des divergences d'opinions voire des clivages interdisciplinaires mais également de bénéficier de contributions croisées de disciplines épistémologiquement distantes. Ce sont également les temporalités de l'agir qui diffèrent entre l'interventionnisme instinctif du somaticien et du soin apporté au corps dans les phases de dénutrition ou de complications somatiques aiguës, parfois en occultant (parfois par nécessité) la prépondérance de la comorbidité psychiatrique et du soin à y apporter, et le nécessaire attentisme de l'approche psychiatrique ou psychothérapeutique pris dans le déroulé du soin psychique et laissant (parfois par nécessité) le "corps" aux somaticiens (Vincent, 2009). Concernant les modalités thérapeutiques institutionnelles, notamment durant les phases d'hospitalisation, chaque discipline intervient conjointement et de façon coordonnée mais selon des temporalités variables avec une intensification des soins spécifiques (somatiques, nutritionnels, psychiques) selon la prépondérance de la symptomatologie présentée par le patient. Néanmoins toutes les phases de soins bénéficient du regard croisé et des compétences des différentes disciplines venant soutenir les décisions thérapeutiques, notamment pour les situations complexes, sont prises dans un espace de réflexion commun qui se situe "entre, au-delà, et au travers" des disciplines. L'une des spécificités institutionnelles est d'avoir pensé, pour chaque unité fonctionnelle, mais également entre les unités fonctionnelles, des temps et des lieux d'échanges et de partage où chaque discipline est représentée, permettant un accordage permanent des points de vue et de s'extraire des schèmes cognitifs propres à chaque discipline. Il ne s'agit pas là d'une approche interdisciplinaire où chaque acteur reste dans le confort et

les représentations de l'objet appartenant à son champ disciplinaire, mais d'opérer un mouvement aux limites de sa discipline pour se laisser traverser par les savoir autres. Une autre spécificité qui permet à l'adolescent et sa famille d'investir durablement les soins, et limite le risque de rupture de soins intra ou extra-institutionnels, est la désignation d'un médecin coordonnateur (pour la plupart des patients il s'agit d'un médecin de l'adolescence) qui l'accompagnera sur son parcours de soin, et favorisera la construction initiale et le maintien de l'alliance thérapeutique, garantissant le cadre et la continuité des soins (Haute Autorité de Santé, 2010 ; Haute Autorité de Santé, 2019).

iii. Les partenaires et réseaux

Le champ TCA institutionnel proprement dit, représenté par le système de soins et les différents acteurs impliqués construit autour du patient, s'est enrichi au fil du temps de multiples collaborations avec d'autres partenaires extra-institutionnels, tels que les professionnels des réseaux de l'ANMDA, du Réseau TCA Francilien ou du Réseau National (FFAB) favorisant la réalisation de projets collaboratifs dans le domaine du soin et de la recherche. D'autres acteurs tels que les associations d'usagers, ou les organismes de tutelle publique, apportant d'autres niveaux de savoir et de nouvelles interactions génèrent d'autres niveaux de réalité dans ce système complexe. La parole des usagers, les décisions en matière de politique de santé (durée de séjour, remboursement des soins, structures de soins de suite, construction filière spécialisée) interagissent de façon indirecte avec l'objet au travers de la réalité institutionnelle et du système de soins, ou au travers des interactions créées avec les familles et l'entourage (groupe de paroles, associations d'usagers).

iv. La coordination des soins

Dans ce système complexe, incluant de multiples sous-systèmes qui constituent le champ TCA tel que nous l'avons décrit, la notion de coordination nous apparaît

centrale dans la prise en charge de ces pathologies chroniques et évolutives dont le parcours de soin est constitué d'étapes et de rencontres avec des acteurs provenant d'univers multiples, se déroulant dans des unités de lieux successives intra et extra-institutionnelles. La coordination des soins a, entre autres objectifs, de favoriser l'articulation des soins entre les différentes disciplines et d'accompagner le patient souffrant de TCA et sa famille au cours des étapes successives du parcours patient. Cette fonction est particulièrement nécessaire lors de certaines phases de vulnérabilité tel que le processus de transition entre milieu de soin adolescent et adulte propices aux ruptures de soin et aux réaggravations symptomatiques (Blanchet-Collet, et al., 2017). La désignation d'un médecin coordonnateur, garant du cadre et de la continuité des soins, ayant la volonté de s'investir sur une durée prolongée auprès de l'adolescent, de sa famille et des autres acteurs du champ TCA, favorise la construction de l'alliance thérapeutique individuelle et familiale, mais permet également d'assurer la liaison transversale entre les unités pour accompagner la trajectoire institutionnelle et faciliter les liens extra-institutionnels. Enfin le rôle du médecin coordonnateur est de participer à la construction de la filière de soin TCA et garantir son intégration et son articulation avec le projet de soin institutionnel global.

c. LE CONCEPT NOMADE de TRANSDISCIPLINARITE

Dans la période d'hypermodernité actuelle, les politiques de Santé en France et les recommandations dans de nombreux domaines (soin, éducation, recherche et politique), mettent l'accent sur la nécessité de rassembler et de favoriser les échanges entre les disciplines (Choi, & Pak, 2006). Ces rencontres et interactions disciplinaires sont décrites par de nombreux concepts en désignant les modalités et les niveaux d'interactions. Parmi ces concepts¹⁹, le terme de transdisciplinarité se présente comme un "concept nomade" (Stengers, 1987)

¹⁹ cf tableau 2 concernant la classification des concepts polydisciplinaires.

utilisé dans de nombreux contextes et domaines, éveillant la curiosité des professionnels et des scientifiques et donnant parfois sans fondement un pseudo cadre conceptuel ou une sorte de “caution scientifique” aux propos de celui qui les tient. En réalité, le plus souvent le concept de transdisciplinarité se présente comme un terme polysémique, interchangeable avec les termes de multi-, inter-, pluridisciplinarité. La confusion qui règne autour de la signification de ces termes, et l’amalgame qui en est fait, a été nommée “bourbier sémantique” par certains auteurs (Leathard, 1994, cité par Choi, & Pak, 2006, p 352). De fait, le terme de transdisciplinarité a également progressivement envahi le langage des différents intervenants, professionnels, usagers, politiques, impliqués directement ou indirectement auprès des patients souffrant de TCA; son utilisation apparaissant le plus souvent aléatoire et régulièrement détournée de son sens initial.

C’est dans le vécu institutionnel quotidien auprès des patients souffrant de TCA et de leurs familles, au cœur de la pratique clinique et des collaborations multiples qu’est survenu le besoin de décrire cet espace complexe. Il s’agissait alors de saisir et de pouvoir identifier les courants qui nous traversaient et de pouvoir décrire ce que nous avions créé, presque à notre insu. La nécessité de rattacher ce champ à un concept pouvant rendre compte de la réalité des acteurs et interactions multiples s’est rapidement imposée. Le concept de transdisciplinarité nous a semblé le plus adapté au projet qui se dessinait. L’idée de privilégier le concept de transdisciplinarité à d’autres termes tels que les concepts de multi-, pluri-, interdisciplinarité reflétant d’autres types d’interactions disciplinaires, semblait être justifié par les raisons suivantes : la position du concept de transdisciplinarité dans la gradation des interactions disciplinaires, où la transdisciplinarité apparaît comme une étape ultime dans la progression des niveaux d’échanges entre disciplines ; le haut niveau de complexité rattaché au concept de transdisciplinarité faisant écho à la complexité de l’objet TCA et à la multitude d’interactions et d’acteurs impliqués dans la pratique institutionnelle et plus largement dans le champ des TCA ; enfin parce que les premières lectures faisant état d’un concept de transdisciplinarité

pouvant être défini comme une “nouvelle position intellectuelle dirigée vers la compréhension du monde” (Nicolescu, 1996) nous semblait adaptée à la dimensions mystiques et humanistes qui sont rattachée à l'épistémologie des figures anorexiques et à celle des approches collectives, mais également à la place accordée aux sciences humaines aux côtés des disciplines médicales dans l'espace de soin et de recherche pour les TCA.

L'auteure a donc souhaité s'extraire de sa position de médecin clinicien, et de ses fonctions de médecin coordonnateur pour investir une posture de recherche visant à explorer le concept de transdisciplinarité et à évaluer sa nécessité pour décrire une pratique institutionnelle construite autour des adolescents souffrant de TCA et plus largement de sa pertinence dans le champ des TCA.

III. OBJECTIFS

Nous proposons dans ce travail de thèse d'étudier la place de la transdisciplinarité dans le champ des troubles des conduites alimentaires et d'évaluer la pertinence de ce concept émergent pour le décrire. Ce projet a nécessité un certain nombre d'étapes qui sont les suivantes:

- Préciser le concept de transdisciplinarité
- Décrire une pratique institutionnelle autour de l'objet TCA
- Relier le concept de transdisciplinarité au système complexe des TCA
- Proposer des applications de la transdisciplinarité.

Ce travail comporte à la fois une partie théorique de recherche sur le concept de transdisciplinarité (analyse conceptuelle et réflexion épistémologique, hypothèse) et une partie empirique issue de la recherche transdisciplinaire (description d'une pratique clinique institutionnelle, applications de la transdisciplinarité illustrées par des données de recherche dans le domaine de la compréhension et du soin).

L'objectif principal de notre travail est le suivant :

- montrer la pertinence du concept de transdisciplinarité pour décrire le champ des TCA (Article 3).

Les objectifs secondaires de notre travail sont les suivants:

- montrer l'aspect heuristique de cette hypothèse par des applications dans de recherches transdisciplinaires dans les domaines de la compréhension (Article 1) et des soins pour les sujets souffrant de TCA (Article 2).
- ouvrir sur la perspective d'une modélisation de la transdisciplinarité dans le champ des TCA (Article 3).

METHODE

METHODE

La méthode utilisée dans ce travail de thèse comporte une partie empirique et une partie théorique qui rendent compte de l'investissement clinique institutionnel dans une Maison des Adolescents de l'auteure, de son travail de réseau et d'autre part de son activité de recherche dans le "champ des TCA". Notre travail est né de ces différents niveaux de réalité, et c'est la confrontation de ces données cliniques, expérientielles et d'accumulation de connaissances théoriques véhiculées "entre, au travers, et au-delà" les frontières disciplinaires qui ont guidé notre démarche. La proposition de modélisation du "champ TCA" qui clôturera ce travail peut être considéré comme un aboutissement (en ce qui concerne ce travail et non pas comme un aboutissement ultime), se situant "entre, au-delà et au travers" les frontières de notre connaissance scientifique et théorique "du dehors" (*épistémé*) et de notre connaissance globale "du dedans" (*gnose*) qui inclut l'intuition et l'imagination (Paul, 2001). La modélisation proposée pourrait ainsi être considérée comme le produit de la dialectique du savoir conscient et inconscient de l'auteure.

La partie empirique concerne :

- une partie descriptive issue de l'expérience de l'auteure à partir de son vécu professionnel, et des éléments empiriques accumulés au cours de l'apprentissage de la transdisciplinarité, amorçant l'ébauche d'une approche réflexive
 - activité de soins (expérience clinique de la transdisciplinarité auprès des adolescents et de leurs familles dans les soins ambulatoires et en hospitalisation)
 - travail institutionnel (construction de la filière de soins pour les patients souffrant de TCA, articulation de tous les acteurs)

du système de soin en consultation, en hôpital de jour et en hospitalisation temps plein)

- travail de réseau (ANMDA, Réseau TCA Francilien, FFAB-FNA TCA).
- une partie recherche dans les groupes de travail de la Fédération Française Anorexie Boulimie (FFAB) qui illustre la pensée et l'action transdisciplinaire dans le cadre de recherches concernant les traitements médicamenteux de l'AN et un modèle intégratif étiopathogénique de l'AN.

La partie théorique concerne :

- le travail d'analyse conceptuelle autour du concept de transdisciplinarité qui a nécessité des recherches bibliographiques dans le domaine des sciences humaines et également de la médecine
- le travail de réflexion épistémologique qui s'est organisé autour de deux axes principaux :
 - l'objet anorexique et son évolution au fil des époques permettant de décrire "les figures anorexiques" et les différents modèles proposés par les sciences humaines (anthropologie, sociologie, psychologie, philosophie)
 - les approches collectives thérapeutiques rendant compte de l'évolution de la philosophie des soins et de la construction des approches transdisciplinaires pour les patients souffrant de TCA.

La dialectique entre partie empirique et théorique :

- Ce travail inclut une partie de modélisation d'une pratique clinique

institutionnelle mise en œuvre depuis une quinzaine d'années à la Maison des Adolescents de l'hôpital Cochin (Maison de Solenn). Ce modèle, qui sera illustré par une représentation schématique, présente les relations entre les éléments d'un système complexe et permet de proposer une image d'une partie du réel autrement non perceptible.

- Nous proposons une modélisation structurale (une vision synchrone indépendante du temps mais basée sur une genèse) du "champ TCA". Notre modèle ne représente pas la réalité, mais vise à sa compréhension, et est issu d'éléments empiriques et d'éléments théoriques, qui nous ont permis de penser l'espace complexe du "champ des TCA" construit autour d'un objet complexe qu'est le sujet souffrant de TCA. "Le modèle est provisoire, selon l'évolution des connaissances, et toujours plus simple que l'objet et plus pauvre que la réalité représentée" (Willett, 1996).

Les difficultés méthodologiques rencontrées au cours de ce travail résident dans la nécessité d'explorer des champs de connaissance très vastes, et donc des bases de données multiples, en sciences humaines (psychologie, anthropologie, philosophie, sociologie), en médecine (psychiatrique, médecine somatique, nutrition) et d'utiliser des supports multiples issus de la littérature des figures anorexiques (romans, récits autobiographiques, témoignages de proches) ou de leur filmographie. Il s'est en effet révélé nécessaire de compléter les recherches bibliographiques réalisées à partir des moteurs de recherche habituels (PubMed, PsycINFO, Google Scholar, Cairn, Theses.fr, OpenGrey), par une exploration analogique d'articles, ouvrages littéraires ou essais visant à enrichir notre analyse conceptuelle et notre réflexion épistémologique en matière de TCA.

Pour des raisons inhérentes à la réalité du travail de recherche et de l'investissement de l'auteure dans des groupes de travail transdisciplinaire ainsi qu'aux exigences de publication scientifique, l'organisation de ce manuscrit est la

suivante : les deux premiers articles concernent l'activité de recherche transdisciplinaire, le troisième article présente une réflexion théorique sur la transdisciplinarité. Chaque présentation d'article débute par une contextualisation du travail effectué et se termine par la contribution spécifique apportée à la démarche globale de l'auteur.

RESULTATS

ARTICLE 1

Un MODELE TRANSDISCIPLINAIRE de COMPREHENSION de l'ANOREXIE MENTALE

Le premier article est une proposition de modèle transdisciplinaire explicatif de l'anorexie mentale. Il a été publié en Juin 2016, dans la revue *Frontiers in Neurosciences* (revue indexée dans Medline, Impact Factor 2019 : 3.648).

Les modèles de compréhension de l'anorexie mentale de l'ère médicale ont bénéficié d'une évolution fulgurante en un siècle ; l'affrontement des théories organogénétiques et psychogénétiques a laissé la place au rassemblement des compétences disciplinaires qui s'impose actuellement comme un paradigme incontournable pour mieux saisir la complexité étiopathogénique des TCA.

Cet article a été conçu dans un environnement transdisciplinaire qui est un groupe de recherche relié à la Fédération Française Anorexie Boulimie²⁰ créée en 2012, auquel l'auteure a pris part, regroupant médecins cliniciens et chercheurs fondamentaux, croisant les données empiriques issues de la recherche clinique auprès des patients souffrant de TCA aux données issues des recherches fondamentales en biologie ou en neurosciences provenant notamment des études sur les modèles murins d'anorexie (Méquinion, Chauveau, & Viltart, 2015 ; Viltart, Duriez, & Tolle, 2018).

²⁰ Le Groupe de Recherche Transdisciplinaire de la Fédération Française Anorexie Boulimie (FFAB-R) correspond à l'ex-Groupe de Recherche Interdisciplinaire de l'Association Française pour le Développement des Approches Spécialisées pour les TCA (GIR-AFDAS-TCA). Le GIR-AFDAS-TCA a été renommé FFAB-R dont l'acronyme a une double lecture en langue Française et Anglaise (French Federation Anorexia Bulimia-Research).

Il s'agit d'un article consensuel proposant un modèle intégratif étiopathogénique de l'anorexie mentale, où l'articulation des contributions respectives de chaque discipline (endocrinologie, nutrition, psychiatrie, génétique et neurosciences) a permis de construire un modèle holistique rendant compte de la multiplicité de facteurs interdépendants impliqués dans le genèse et le maintien de ces troubles. La contribution originale de chaque auteur visait un double objectif : proposer une approche spécialisée partant de son domaine d'expertise mais également envisager que cette approche puisse trouver une légitimité et s'articuler avec les autres approches disciplinaires pour construire un modèle explicatif cohérent.

Ce travail a nécessité à la fois un choix affirmé partant de son propre ancrage disciplinaire et une flexibilité cognitive permettant de construire son approche pour la rendre compatible avec les autres positions disciplinaires. Il s'agit bien là d'une approche transdisciplinaire où chaque auteur est sorti aux frontières de sa propre discipline pour se laisser traverser par les autres hypothèses étiopathogéniques.

La contribution de l'auteure porte sur la création d'un système qui considère la sphère pondéro-nutritionnelle (facteurs bio-anthropométriques et héréditaires mais également environnementaux et psychiques) comme déterminante dans la construction des conduites alimentaires (Birch, 1999). Cette sphère pondéro-nutritionnelle est un système incluant différents éléments comme les interactions précoces mère-enfant, la construction du goût depuis les étapes *in utero*, les conduites alimentaires familiales, l'existence de TCA précoces ou d'autres troubles nutritionnels de la petite enfance. Faisant référence aux théories psychosomatiques, l'hypothèse de l'auteure est que la fragilité innée ou acquise de cette sphère "pondéro-nutritionnelle", serait la cible privilégiée attaquée par le processus pubertaire ("the mismatching team") favorisant l'émergence d'un TCA à l'adolescence ou au début de l'âge adulte. Cette approche renvoie à la question du "choix d'organe" ou de "choix de la fonction" comme

vulnérabilité propre à l'individu dans une pathologie anorexique qui peut être considérée comme trouble psychosomatique (Dejours, 1997).

Cet article illustre l'apport considérable que constitue l'approche transdisciplinaire qui favorise la créativité et permet de saisir la complexité des mécanismes impliqués dans la survenue mais également dans l'auto-entretien du trouble anorexique ; légitimant en miroir l'approche transdisciplinaire dans le domaine du soin. Cette ébauche de modèle théorique se voit confirmée par les études récentes qui présentent l'anorexie mentale comme une pathologie "métabo-psychiatrique" (Anorexia Nervosa Genetics Initiative, et al., 2019).

La contribution spécifique de l'auteure a fait l'objet d'une communication affichée au congrès Européen de l'ECED en Septembre 2017 à Heidelberg (Allemagne) : "The pubertal process and pondero-nutritional-eating basements: the mismatching team". C. Blanchet.

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Specialty section:

This article was submitted to
Neuroendocrine Science,
a section of the journal
Frontiers in Neuroscience

Received: 25 February 2016

Accepted: 23 May 2016

Published: 29 June 2016

Citation:

Gorwood P, Blanchet-Collet C,
Chartrel N, Duclos J, Dechelotte P,
Hanachi M, Fetissov S, Godart N,
Melchior J-C, Ramoz N,
Rovere-Jovene C, Tolle V, Viltart O and
Epelbaum J on behalf of the
GIR-AFDAS-TCA Group (2016) New
Insights in Anorexia Nervosa.
Front. Neurosci. 10:256. doi:
10.3389/fnins.2016.00256

New Insights in Anorexia Nervosa

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Anorexia nervosa (AN) is classically defined as a condition in which an abnormally low body weight is associated with an intense fear of gaining weight and distorted cognitions regarding weight, shape, and drive for thinness. This article reviews recent evidences from physiology, genetics, epigenetics, and brain imaging which allow to consider AN as an abnormality of reward pathways or an attempt to preserve mental homeostasis. Special emphasis is put on ghrelin-resistance and the importance of orexigenic peptides of the lateral hypothalamus, the gut microbiota and a dysimmune disorder of neuropeptide signaling. Physiological processes, secondary to underlying, and premorbid vulnerability factors—the “pondero-nutritional-feeding basements”—are also discussed.

Keywords: eating disorders, reward system adaptations, microbiota, autoantibodies, susceptibility factors, mental homeostasis

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder defined as an abnormally low body weight associated with intense fear of gaining weight and distorted cognitions regarding weight, shape, and drive for thinness (American Psychiatric Association, 2013). This disorder has a 12-month prevalence rate of 0.4% among females, and is characterized by the highest mortality rate of all psychiatric disorders (Harris and Barraclough, 1998) and exceptionally high relapse rates (Zipfel et al., 2000).

The research on anorexia nervosa has historically focused on pituitary glands (Gull, 1888), psychiatric aspects associated with a minimum of 12kg voluntary loss (Bliss and Branch, 1960), or hormones such as oestradiol, progesterone, and LHRH (Boyar et al., 1974), but the aetiology of AN is still unknown, while its development, progression and outcome are considered as clearly influenced by biological, sociocultural, and psychological factors. At the biological level, increased

levels of AgRP, NPY, and Ghrelin were, for example, considered as driving the rewarding aspects of thinness, while decreased levels of BDNF, Oxytocin, TRH, VP, Leptin, and PYY have been related to the abnormal satiety feedback observed in AN (Tortorella et al., 2014). But with the progress of brain imaging techniques (especially functional MRI), GWAS and epigenetic approaches, animal models, discovery of neuropeptides (such as 26RFa), and increased knowledge in the role of gut microbiota, it now appears possible to propose more comprehensive models of AN, which also take into account the improved knowledge of psychological risk factors during (or even before) childhood, and the new insights given by the high psychiatric co-morbidity rate of AN. The present review collection proposes seven short contributions, based on these different approaches, in order to propose a tentatively holistic model of AN, based on the concept of homeostasis disruption both at the level of the body (neuroimmunoendocrine approaches), the brain (imaging), and the mind (psychological and clinical approaches).

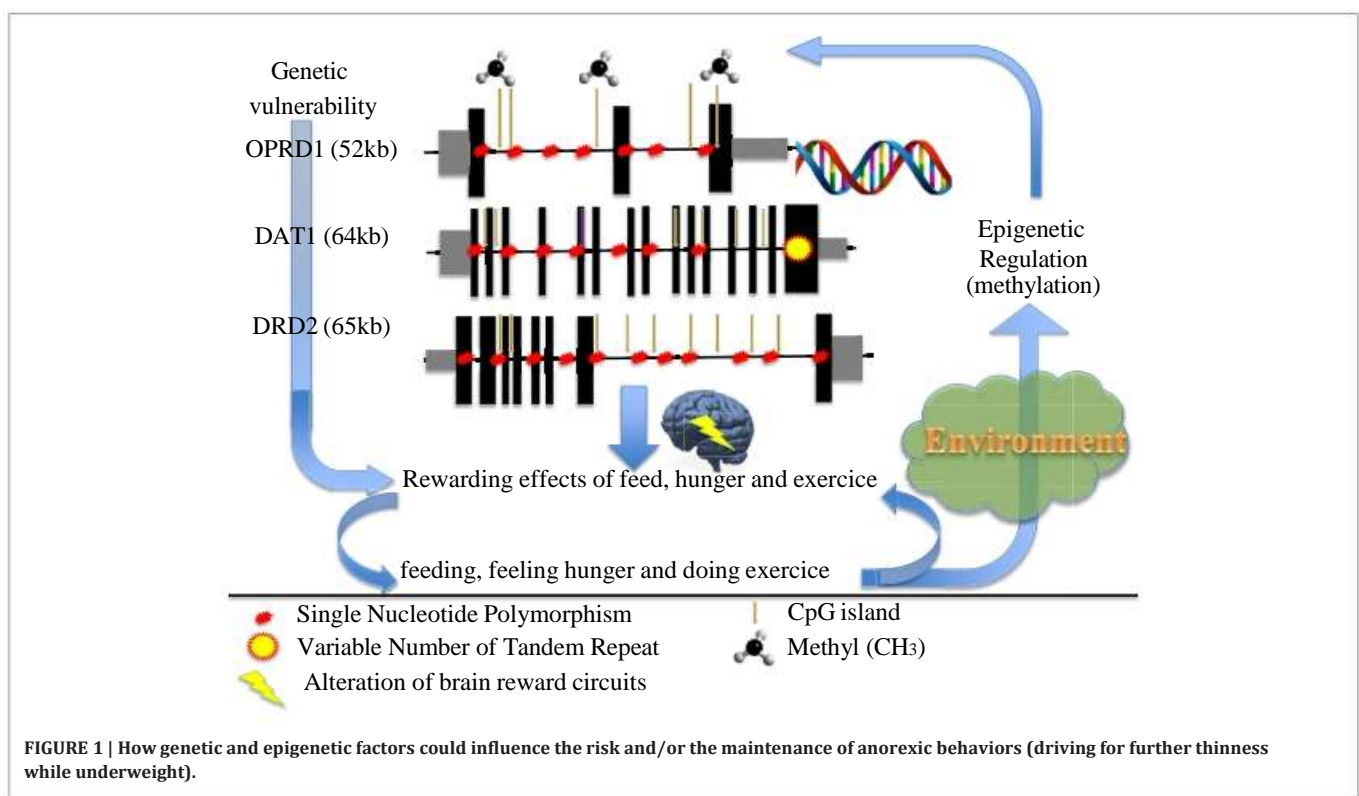
MODEL 1: ANOREXIA NERVOSA IS AN ABNORMALITY OF REWARD PATHWAY: EVIDENCES FROM PHYSIOLOGY, GENETICS, EPIGENETICS, AND BRAIN IMAGING

Since three decades, physiological evidences support the hypothesis that anorexia nervosa (AN) can be considered as a starvation addiction, driven by abnormalities of the food reward

pathway. Novel tools from molecular genetics and brain imaging supplied more evidence supporting this pathophysiological hypothesis.

Numerous opioid neuropeptides have been identified and characterized as being involved in the regulation of vital functions, such as appetite and reproduction, conferring them reward properties, apparently as highly addictive as the exogenous opiates (Le Merrer et al., 2009). The addiction theory in eating disorders is therefore supported by the fact that both appetite dysfunction (starvation and bingeing) and intense physical activity stimulate endorphin activity in 80% of AN patients (Kaye et al., 1989). In 1982, Kaye et al. reported that the opioid activity from the cerebrospinal fluid was significantly higher in underweight AN patients compared to controls. In contrast, this activity decreases in AN patients with a restored weight or in recovered cases compared to controls (Kaye et al., 1982). Furthermore, the plasma levels of codeine and morphine were reported as significantly elevated in AN patients compared to a control group (Marrazzi et al., 1997). These endogenous opioids could be released during the first diets, the feedback control of opioids then reinforcing the associated starvation process in some at-risk subjects. Indeed, peripheral endorphins may foster survival in starvation conditions by conservation of nutrients and water and by decreasing energy-expending activities (Margules, 1979).

Functional brain imaging study analyzing a simple monetary reward task has shown that healthy women had different striatal activity for positive vs. negative feedbacks, while recovered AN patients did not (Wagner et al., 2007). This study supported



the hypothesis of an altered reward process in AN. Another functional brain imaging study demonstrated the existence of an increased salience attribution to rewarding and aversive food stimuli in recovered AN patients (Cowdrey et al., 2011). Structural brain imaging also disclose alteration in the brain regions that are involved in reward circuitry in AN patients, and even in recovered ones (Frank et al., 2013). Recent evidence more precisely showed that patients with AN differ from controls as they favor delayed rewards (larger and later instead of smaller and sooner monetary rewards), being the only one to have an increased activity of the ventral striatum for such rewards (Decker et al., 2015). Finally, two functional brain imaging studies based on the evaluation of visual stimuli depicting a female body with underweight, normal weight, and overweight canonical whole-body features, assessed brain activity with a “feel” task (in a self-referring way) and a “weight” task, as a control task (Fladung et al., 2010, 2013). No difference between AN patients and controls was reported for the “weight” task. In contrast, opposite score for the “feel” task was observed for both adult and adolescent AN patients compared to healthy subjects. Most interestingly, the functional activity of the ventral striatum was significantly higher in AN patients for underweight features (compared to controls) and dramatically reduced for normal body features in adults (Fladung et al., 2010). Similar trends were observed when adolescent were analyzed (Fladung et al., 2013). These studies support once again the existence of an alteration of the reward circuitry in AN, likely due to a reinforcing effect of starvation, due to an increased hedonic feeling of underweight, and a decreased positive feeling of normal bodyweight. Another candidate to explain abnormal reward process is excessive exercise, which is observed in 80% of patients with AN (Davis et al., 1997). In the largest GWAS performed up to now on AN, two SNPs were marginally associated with the disorder ($p = 5 \times 10^{-6}$), one of them (rs17030795) being located in PPP3CA, a calcineurin gene which might be involved in human variations in endurance exercise capacity and tolerance (He et al., 2010b). Furthermore, in a rodent study, leptin was influencing the motivational effects of running via dopamine tone (Fernandes et al., 2015), leptin being more depending of DNA methylation (i.e., under epigenetic regulation) rather than direct genetic control (Tremolizzo et al., 2014).

Interestingly, one of the first AN genome-wide linkage study, performed in 37 AN families, identified a significant peak on chromosome 1p33-36, containing HTR1D and OPRD1 genes, respectively encoding for 1D serotonin receptor and opioid delta receptor. Furthermore, individual variants and haplotypes within both HTR1D and OPRD1 genes were associated with AN in a candidate gene study performed on 191 AN patients and 98 controls (Bergen et al., 2003). The role of the OPRD1 gene in anorexia nervosa was replicated in an independent study comparing 226 AN patients to 678 controls (Brown et al., 2007). Lastly, a genome-wide association study performed on 1033 AN patients vs. 3733 controls confirmed that a common variant of OPRD1 gene is indeed associated with AN (Wang et al., 2011), although not in the more recent GWAS which was performed on a larger sample (Boraska et al., 2014).

The level of opioids in the nucleus accumbens (NA) critically regulates the release of dopamine. A positron emission tomography performed on 10 recovered AN patients and 12 controls reported an increased binding of dopamine D2/D3 receptors in the anterior ventral striatum, which contains the NA (Frank et al., 2005). This difference could be due to either an increase of density and/or affinity of the D2/D3 receptors in the NA, or a decrease of dopamine level in AN. It is thus possible that AN patients reduce their food intake because of abnormalities of dopamine dysfunction, i.e., of the reward brain circuit, transmitting an anxiogenic signal instead of an expected hedonic one. Genetic variants of the DRD2 gene, including -141C Ins/Del previously shown to modify transcription level, were associated with AN (Bergen et al., 2005). Furthermore, a significant higher percentage of methylated promoter of DAT1 and DRD2 genes was observed in AN patients compared to controls, and such methylation were associated with a increased expression of the DAT1 gene and a decreased expression of the DRD2 gene (Frieling et al., 2010). Thus, potential genetic and epigenetic dysregulations of the dopamine reward circuit in patients reinforce its role in the pathophysiology of AN. In addition, the receptor of the hunger hormone ghrelin is able to form heterodimers with DRD2 in hypothalamic neurons, potentially promoting anorexigenic behavior (Kern et al., 2012).

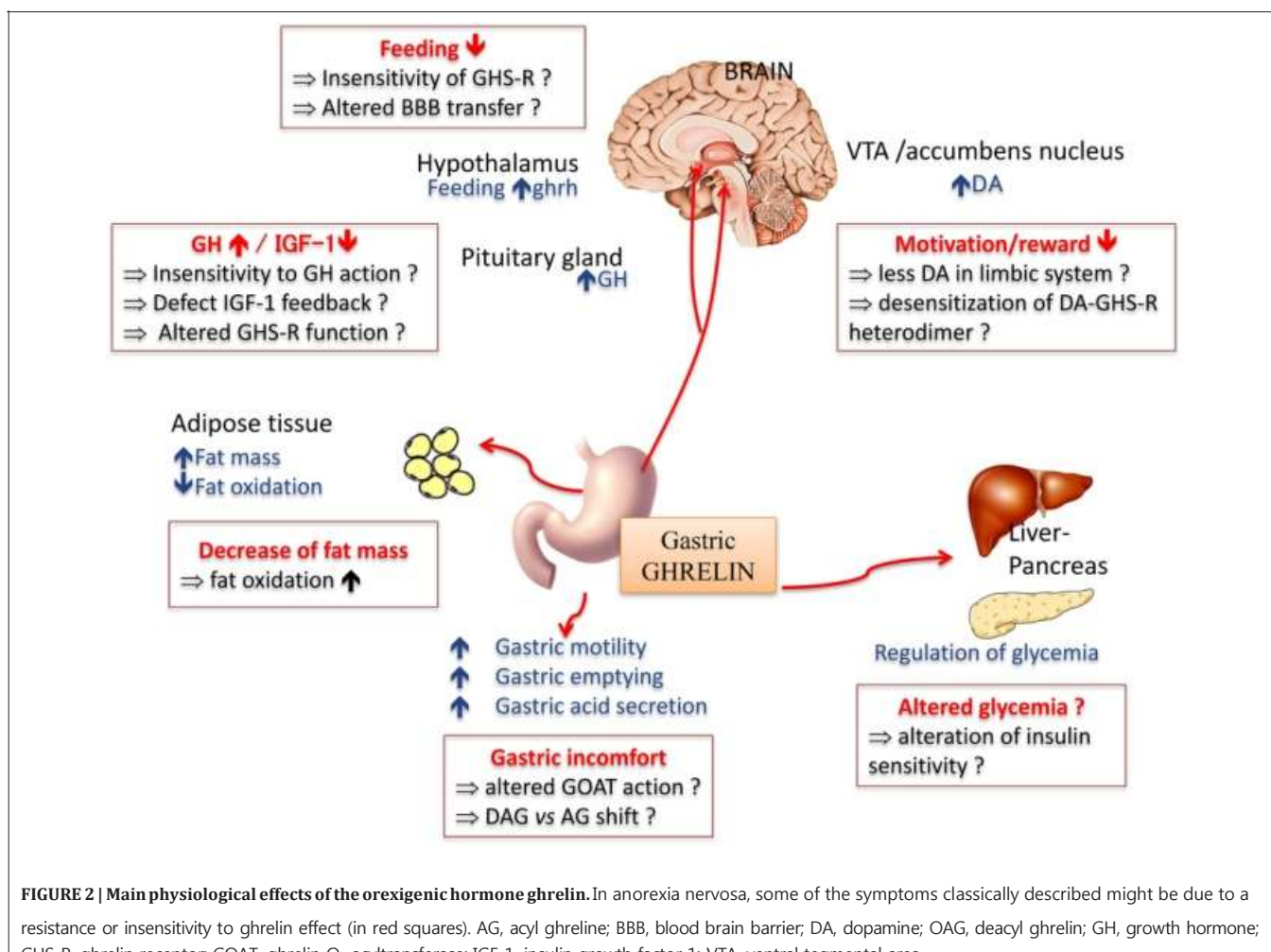
To conclude (**Figure 1**), we propose that anorexia nervosa results from dysregulation(s) of the balance between input (feeding/hunger) and output (excessive exercise), also at the genetic and/or epigenetic levels, of the dopamine genes involved in (1) the reward circuitry, located in the ventral striatum, and (2) the food regulatory mechanism, located in the hypothalamus, to alter these processes and confer starvation dependence.

MODEL 2: ANOREXIA NERVOSA IS A GHRELIN-SPECIFIC RESISTANCE?

AN patients exhibit changes in the release of hormones involved in energy metabolism and regulation of feeding behavior (Germain et al., 2007; Hasan and Hasan, 2011). In particular plasma levels of ghrelin, an orexigenic hormone mostly released from the stomach (Cummings et al., 2001), are increased (Germain et al., 2009, 2010). Such an increase seems paradoxical in light of the restrained eating adopted by these patients, but may be adaptive by a feedback mechanism due to the lack of nutrients. Several groups have proposed the concept of ghrelin-resistance that reflects the inability of increased ghrelin to induce appetite in AN patients, thereby creating a metabolic vicious circle maintained by their food restriction behavior. In this context, the ghrelin system should be considered as a valuable therapeutic target in eating disorders.

Ghrelin Is Derived from a Unique Prohormone Coding Various Peptides Involved in Feeding-Oriented Behaviors

Amongst peripheral factors sensitive to nutritional, hedonic and emotional signals, proghrelin is a unique prohormone encoding several peptides with structural and functional



heterogeneity (Hassouna et al., 2010). Ghrelin is synthesized from the stomach (Kojima et al., 1999; Tomasetto et al., 2000) and was initially identified as an endogenous ligand for the growth hormone (GH) secretagogue receptor (GHS-R1a). In addition to its primary effect as a GH secretagogue (Tolle et al., 2001), ghrelin exerts pleiotropic effects both peripherally and centrally (Figure 2), including the modulation of the dopaminergic reward system (for review see Méquinion et al., 2013). Other naturally occurring variants of ghrelin are desacyl ghrelin (DAG), which is the most abundant form in plasma and accounts for 80–90% of total ghrelin (Kojima and Kangawa, 2005) and obestatin, another bioactive peptide initially described for its anorectic actions in rodents (Zhang et al., 2005).

Clinical Evidence of Ghrelin-Resistance

Plasma acyl ghrelin (AG) levels are elevated in AN with a pure restrictive type (AN-R) (Germain et al., 2009, 2010). Investigations of pharmacological effects of ghrelin in patients with AN are not conclusive as yet. Indeed, intravenous infusion of ghrelin during 5 h induced no clear changes in food intake, but increased sleepiness (Miljic et al., 2006). A sensation of hunger was shown in six of nine patients with

AN after a bolus intravenous injection of 1 mg/kg ghrelin (Broglia et al., 2004) similarly to normal subjects (five of seven responders). Another study demonstrated that administration of ghrelin (3 mg/kg) twice a day decreased gastrointestinal symptoms and increased sensations of hunger and daily energy intake (12–36%) on five AN patients (Hotta et al., 2009). In these pilot studies, the true effect of ghrelin remains difficult to assess due to the lack of proper controls, the small number of treated patients, difficulties to properly evaluate the real motivation of patients to eat and the route and frequencies of ghrelin and/or agonists administration (Ueno et al., 2010).

If Ghrelin-Resistance Exists, Where and How Does It Occur?

The inability of AN-R patients to respond to elevated ghrelin levels could be due to: a reduced ability to be transported to central targets within the hypothalamus (Schaeffer et al., 2013); a reduced GHS-R sensitivity or function; a dysregulation of hypothalamic NPY/AgRP and POMC neurons, direct or indirect targets of ghrelin effects, exerting opposing actions on food intake (Denis et al., 2014); an alteration in the ghrelin

signaling on dopaminergic neurons, in the ventral tegmental area (VTA) (Abizaid et al., 2006), a structure involved in the reward/locomotion behavior, and hypothalamus to modulate appetite, respectively (Jiang et al., 2006; Kern et al., 2012; Sharpe et al., 2016).

Ghrelino-Resistance: Antagonism by Other Ghrelin-Derived Peptides?

The hypothesis of a ghrelino-resistance in AN-R requires further evidence that (1) endogenous ghrelin is important in stimulating appetite and (2) other ghrelin-derived peptides might be modulators of AG actions in animal models and AN patients.

In mice with total ghrelin deficiency or selective AG deficiency, food intake is not reduced (Sun et al., 2003, 2004; Zigman et al., 2005; Pfluger et al., 2008; Zhao et al., 2010). This does not seem to support a key role of AG in homeostatic eating. However, suppressed intake of rewarding food in a free choice food paradigm, lack of cue-potiated feeding and suppressed motivation for food in an operant responding model rather support a role of the endogenous peptide(s) in hedonic eating (Uchida et al., 2013).

DAG may be an important modulator of appetite by counteracting AG actions as demonstrated after central or peripheral injections (Asakawa et al., 2005; Inhoff et al., 2008). Interestingly, transgenic mice overexpressing DAG display significantly reduced body weight, reduced food intake and body fat mass and moderately decreased linear growth compared to non-transgenic mice (Asakawa et al., 2005). In addition, DAG exerts several biological actions, independent of the GHS-R pathway, including regulation of glucose homeostasis and fat metabolism (Delhanty et al., 2012, 2013). Although obestatin was initially reported to decrease appetite and weight gain thus opposing ghrelin's effects by acting on an orphan receptor, GPR39 (Zhang et al., 2005), controversies rapidly arose concerning the anorexigenic actions of this peptide through GPR39 (Lauwers et al., 2006; Chartrel et al., 2007; Holst et al., 2007; Zizzari et al., 2007; Hassouna et al., 2010, 2012). In AN-R patients, obestatin, and the ghrelin/obestatin ratio were found decreased whereas this ratio was not altered in constitutionally thin women (Germain et al., 2009, 2010). Such changes may participate in the eating restriction despite hyperghrelinemia observed in these patients.

Other Possible Mechanisms to Explain Resistance to Feeding

Ghrelin might also impact non-homeostatic systems that involve more particularly the meso-cortico-limbic system. Skibicka et al. (2013) demonstrated that the significant increase for food motivation/reward behavior observed after a ghrelin injection in the VTA is abolished by a pretreatment with D1-like or D2 receptor antagonist, injected in the nucleus accumbens, the main target of VTA dopaminergic neurons. This brain structure is also involved in the integration of messages from the prefrontal inhibitory circuitry. Indeed, prefrontal cortex is strongly activated in AN patient following presentation of

food images as observed in a fMRI study (Zhu et al., 2012), and alterations in the serotonergic/dopaminergic signaling are also described in these patients (Bailer et al., 2007, 2013). In AN patients, an altered impact of ghrelin on the reward systems might modify the integration of informations related to emotional process associated with food. Due to the paucity of data and the lack of consistent clinical information, the use of animal models to analyze more finely the mechanisms of ghrelin action at different levels of the brain system appears essential.

From Clinics to Bench: What Can We Learn from Animal Models?

A complete animal model of AN does not exist due in part to the neuropsychiatric aspects of the disease (Méquinion et al., 2015b). Such an ideal model of AN would include adolescent onset of the disease, predominance in females, high activity, chronic stress, decreased food intake, and body weight. Moreover, AN is a chronic disease, and most of the murine models described so far maintain a protocol on a short period (few days). Nevertheless, some aspects like food restriction associated with voluntary physical activity or chronic stress can be reproduced in mice models. The model of separation with restricted access to food (separation-based anorexia, SBA), first developed in mice by van Leeuwen et al. (1997), induces a chronic stress that results in an increase of energy expenditure without hyperactivity. Recent data demonstrated that, when this protocol is maintained on the long-term, it induced AN like alterations such as a decrease in bone mineral density (osteoporosis) associated with a dysregulation of leptin signaling (Zgheib et al., 2014). The model of hyperactivity associated with food restriction (activity-based anorexia, ABA), first developed in rats (Hall et al., 1953; Routtenberg and Kuznesof, 1967) and subsequently adapted to mice (Gelegen et al., 2007) is considered as a good animal model of AN as it mimics important features of the disease (Routtenberg and Kuznesof, 1967; de Rijke et al., 2005). The ABA model also emphasizes the involvement of the ghrelin/GHS-R pathway in food anticipatory activities, a behavior also described in AN-R patients (Blum et al., 2009; Scheurink et al., 2010; Verhagen et al., 2011). On a modified long-term ABA model, where food was quantitatively restricted (50% during 10 weeks), symptoms classically observed in AN patients (body weight loss, endocrine changes, oestral cycle loss...) as well as alterations in the integration of the ghrelin message at the hypothalamic levels were observed (Méquinion et al., 2015a).

Conclusion: Is Anorexia Nervosa a Ghrelino-Resistance or an Adaptive Metabolic Response to Denutrition?

In human pathology, the question remains whether ghrelin resistance (or decreased sensitivity) is only limited to the balance between patients' hunger and satiety and motivation to the rewarding aspect of food. Indeed, such hyperghrelinemia can also serve as an adaptive neuroendocrine metabolic response to the disease since ghrelin appears required for the maintenance of blood glucose homeostasis during severe calorie restriction in

mice (Zhao et al., 2010). Thus, up-regulation in ghrelin synthesis may be needed to maintain survival in the restrictive type of AN. However, ghrelin is differentially regulated according to the anorexic subtype as plasma levels are found unchanged in binge-purging anorexic patients, suggesting that both subtypes engage in differential adaptive process to starvation and/or a difference in the perception of hunger and the motivation to eat. Extrapolation from these fundamental observations to the human pathology should be carefully interpreted and will require further exploration and validation of experimental models. Animal models, despite their weakness on some aspects of the disease might permit to assess long term peripheral and/or central alterations due to chronic and drastic food restriction associated or not with activity or chronic stress. Anxiety and hyperactivity behaviors have a significant role in the pathogenesis and progression of the disease. One of the major advantages of using mice as an animal model is that many well-described inbred lines are available to assess the part of genetic or environmental component of anorexia. These animal models will be useful to precisely determine the mechanisms involved in the impaired integration of the ghrelin signal.

MODEL 3: ANOREXIA NERVOSA (AN) IS A CHRONIC STIMULATION OF THE REWARD SYSTEM BY OREXIGENIC NEUROPEPTIDES OF THE LATERAL HYPOTHALAMIC AREA

The hypothalamus plays a pivotal role in behavioral and emotional reactions and contains the major center that regulates feeding behavior. All patients are unable to adapt their feeding

behavior to energy demand and costs, raising the possibility of a dysfunction of the orexigenic and/or anorexigenic neuropeptides regulating appetite within the hypothalamus. Besides, recent evidence support the view that AN might be a pathology of abnormally high reward process for starvation or purging behaviors. For instance, patients recovered from AN still show an increased neural response to both pleasant and aversive food stimuli in brain circuitry mediating reward (Cowdrey et al., 2011). Dopamine is the neurotransmitter of the reward system and several lines of evidence suggest the occurrence of a dysfunctional dopamine-striatal system in AN that might explain the lack of pleasure associated with food intake and the general anhedonia of anorectic patients (Kaye et al., 2009). Supporting this notion, amphetamine-induced dopamine release increases anxiety in individuals recovered from AN (Bailer et al., 2012) and that could explain why food-related dopamine release generates anxiety in AN patients whereas feeding is pleasurable in healthy subjects. Interestingly, the lateral hypothalamic area (LHA), that contains the orexigenic neurons expressing orexins, melanin-concentrating hormone (MCH), and 26RFa, sends projections to the brain reward circuitry (Aston-Jones et al., 2010), suggesting that dysfunction of orexigenic hypothalamic neuropeptides may alter the dopamine reward system in AN.

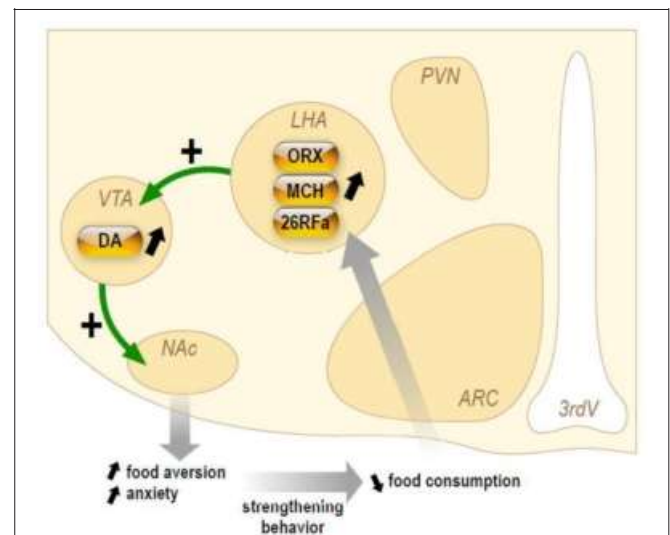


FIGURE 3 | Schematic representation of the hypothetical chronic stimulation of orexigenic neuropeptides on the reward circuitry in anorexia nervosa. Briefly, decrease of food ingestion induces a stimulation of the neuronal activity of the lateral hypothalamic area (LHA) that will release the orexigenic neuropeptides orexins (ORX), melanin-concentrating hormone (MCH), and 26RFa in the ventral tegmental area (VTA). This results in an increase of dopamine (DA) release in the accumbens nucleus (NAc). In anorectic patients, this stimulation of the reward system results in food

aversion associated with enhanced anxiety that will, in turn, reinforce the decrease in food intake.

Herein, we will briefly present (**Figure 3**) the current knowledge on three orexigenic neuropeptides produced by neurons of the LHA in AN, i.e., the orexins, MCH, and 26RFa.

Orexins

Orexins are produced by <80,000 neurons exclusively located in the LHA (Sakurai et al., 1998). Orexin A (OxA) and orexin B (OxB) are two neuropeptides that share 46% identity and are in tandem on the same precursor (Sakurai et al., 1998). Orexins are the endogenous ligands of two G-protein coupled receptors termed OxR1 and OxR2 (Sakurai et al., 1998). Central administration of OxA or OxB stimulates food consumption (Sakurai et al., 1998). Prepro-orexin mRNA is up-regulated following fasting, and conversely down-regulated in ob/ob and db/db obese mice (Sakurai et al., 1998; Yamamoto et al., 1999), whereas orexin deficient mice show robust hypophagia (Hara et al., 2001). Furthermore, systemic administration of the OxR1 antagonist SB-334867 reduces feeding by selectively enhancing the behavioral satiety (Ishii et al., 2004).

Two distinct studies have evaluated the evolution of plasma OxA levels in patients with AN during 2, 3, or 6 months of realimentation (Bronsky et al., 2011; Janas-Kozik et al., 2011). The data obtained are conflicting as the first study (Bronsky et al., 2011) reports a significant increase of fasting plasma OxA concentration in untreated AN patients whereas the second one describes a decrease of circulating OxA in AN subjects before refeeding (Janas-Kozik et al., 2011). However, the two studies observe a progressive decrease of circulating OxA during

realimentation, rather suggesting that the orexin system is up-regulated in AN.

Accumulating data indicate that orexins are involved in reward-based feeding. As a matter of fact, activation of orexin neurons in the LHA is strongly linked to preferences for cues associated with drug and food reward (Harris et al., 2005). Consistent with this, orexin injected into the VTA, that contains the dopamine neurons, increases dopamine release in the accumbens nucleus (NAc), which provides enjoyment and reinforcement to motivate repeated activity, and stimulates intake of a rewarding high fat diet (Zheng et al., 2007). Conversely, OXR1 antagonism in VTA attenuates high-fat feeding in sated rat (for review, Cason et al., 2010). Additionally, central administration of orexin increases self-administration for sweet, an effect that is blocked by OXR1 antagonists, suggesting that orexins promote the reinforcing properties of at least some types of food (Cason et al., 2010).

MCH

MCH is a cyclic peptide predominantly expressed in the LHA. MCH induces food intake after central injections (Qu et al., 1996), and its gene expression is modulated by fasting and in hypoleptinemic ob/ob mice (Qu et al., 1996). Two G protein-coupled (GPCR) MCH receptors (MCH-R1 and MCH-R2) are present in human, of which only MCH-R1 appears functional in rodents (Forray, 2003). Several genetically-modified mice that overexpress or lack MCH (Shimada et al., 1998) or MCH-R1 (Marsh et al., 2002) genes were generated and displayed marked alterations in the regulation of appetite and/or energy balance. At present, the MCH system has never been investigated in AN. However, it is interesting to note that the orexigenic effect of MCH is largely dependent upon its action in the NAc of the reward system. Indeed, injections of MCH and MCH antagonists into the NAc are orexigenic and anorexigenic respectively (Georgescu et al., 2005). MCH injections in this area decrease neuronal firing of spiny neurons and increase hedonic value of sweet foods (Lopez et al., 2011). This suggests that MCH signaling pathways play a complex but important role in feeding-reward control and could provide important information about mechanisms underlying the development of AN.

26RFa

26RFa is a 26-residue RFamide peptide characterized in various vertebrate species including Man (Chartrel et al., 2003, 2011). 26RFa has been identified as the cognate ligand of the human orphan G protein-coupled receptor, GPR103 (Takayasu et al., 2006; Chartrel et al., 2011). Neuroanatomical observations revealed that 26RFa- and GPR103-expressing neurons are primarily localized in hypothalamic nuclei involved in the control of feeding behavior (Chartrel et al., 2003; Takayasu et al., 2006; Bruzzone et al., 2007). 26RFa-containing neurons are exclusively located in the LHA and the ventromedial hypothalamic nucleus (Chartrel et al., 2003). Central administration of 26RFa stimulates food intake and causes obesity in rodents (Chartrel et al., 2003; Moriya et al., 2006; Takayasu et al., 2006). In addition, 26RFa mRNA is up-regulated in the hypothalamus of obese ob/ob and

db/db mice (Takayasu et al., 2006) indicating that the expression of the 26RFa gene is modulated in condition of energy imbalance.

Circadian profile of plasma 26RFa was investigated in AN patients. The data showed that 26RFa levels are significantly increased all over the day in patients with restrictive AN as compared to healthy subjects (Galusca et al., 2012).

Detailed mapping of GPR103 mRNA in the brain revealed that the 26RFa receptor is expressed in the VTA, the amygdala, and the NAc (Bruzzone et al., 2007), suggesting that, in as much the same way as orexins and MCH, 26RFa may be involved in reward-based food intake.

Conclusion

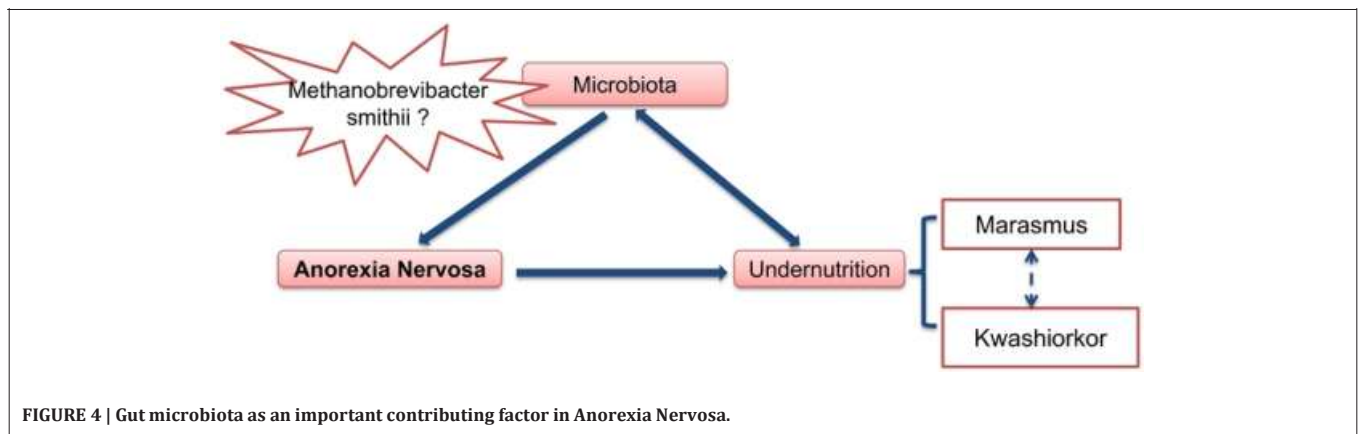
Orexigenic neuropeptides including ghrelin, orexins and 26RFa are up-regulated in AN and it is thought that this orexigenic profile reflects an adaptive mechanism of the organism to promote food intake and thus to counteract undernutrition. However, this adaptive mechanism is ineffective in increasing food consumption leading to the concept of a global resistance of AN patients to orexigenic signals. Here we present an alternate hypothesis. We speculate that a chronic increase of the activity of LHA orexigenic neurons expressing orexins, MCH, or 26RFa could reinforce dopamine-induced anxiety in the reward system of AN patients and thus the aversion to ingest food.

MODEL 4: GUT MICROBIOTA IS A CENTRAL FACTOR IN ANOREXIA NERVOSA

Anorexia nervosa (AN), the most frequent and the most serious eating disorder, is often associated with severe proteino-energetic malnutrition (PEM). Marasmus, the adaptive form of semi-prolonged fasting, is the predominant form of malnutrition associated with AN. However, the kwashiorkor type is present in some cases, and is characterized by a constellation of features including peripheral edema, hypoalbuminemia, fatty liver, skin and hair lesions, apathy, high a relative immuno-depression with high risk of infections. It is associated with a lot of deleterious secondary complications and a high rate of morbidity/mortality. Some patients have a mixed picture of marasmic-kwashiorkor malnutrition.

In the last decades, the role of gut microbiota in different diseases was demonstrated thanks to the development of new methods. The most accurate ones are metagenomics which aims to study all genetic content of prokaryote cells by high throughput sequencing.

With such new tools, the role of gut microbiome was defined on nutrients absorption and energy regulation (harvest, storage, and expenditure of energy). It is now established that the gut microbiome contributes to the risk and pathogenesis of malnutrition through nutrient metabolism and immune function (Krajmalnik-Brown et al., 2012). A clinical trial, comparing 16S rRNA PCR fecal samples of seven malnourished children with seven healthy ones, showed that the former have a significantly lower number of operational taxonomic units in their gut than healthy subjects (310 vs. 546) (Monira et al., 2011). A



metagenomic comparison of gut microbiota, studying 9 well-nourished twin pairs to 13 twin pairs discordant for kwashiorkor, showed a significant difference on gut microbiota profile. Indeed malnourished twins (kwashiorkor) had a considerably less differentiated and immature gut microbiome than healthy or marasmic children (Smith et al., 2013). When stool samples from kwashiorkor-malnourished children were transplanted to gnotobiotic mice, these animals developed weight loss and severe malnutrition (Smith et al., 2013). In a recently randomized controlled clinical trial in 2767 Malawian malnourished children, a 1-week oral antibiotic (which modulates gut microbiota) treatment improved the nutritional status of malnourished children and decreased mortality (Trehan et al., 2013).

Modifications of the gut microbiota have also been described in AN patients. Armougom et al. (2009) measured bacterial divisions of Bacteroidetes, Firmicutes, Lactobacillus, and *Methanobrevibacter smithii*. They compared the feces of 20 obese subjects, 9 patients with AN and 20 normal weight healthy controls. AN patients were moderately undernourished, with an average BMI at 16. All AN patients had an increase of *M. smithii* (Armougom et al., 2009). This Archeon, which comprises up to 10% of all anaerobes in the colon of healthy adults, plays a central role in bacterial digestion of polysaccharides. It recycles hydrogen in methane, allowing for an increase in the transformation of nutrients into calories and thereby increasing energy efficiency (Samuel et al., 2007). It is possible that chronic constipation, which is common in AN patients, could also be present before weight loss and causes the increase of *M. smithii* in their gut (Kim et al., 2012). In addition, by using electrophoretic profile of the 16S RNA microbiota, a deviation of microbiota was found in 8 AN undernourished patients (average BMI at 12) in comparison to nine healthy subjects (Hanachi et al., 2013).

All these data show that there are modifications in gut microbiota of AN patients, not necessarily severely malnourished. These changes include an increase of methanogen archaea directly involved in energy efficiency. Indeed the increase of *M. smithii* can lead to the optimisation of food transformation of nutrients into calories. This increase of *M. smithii* could have preceded undernutrition and could play a central role in the outbreak of anorexia nervosa. In order to explore this pathway

the gut microbiota of patients with AN should be assessed before the beginning of weight loss, during nutritional therapy and after recovery of weight loss.

In summary (Figure 4), at least two hypotheses can be proposed concerning the role of gut microbiota in anorexia nervosa: (1) some pre-existing changes in gut microbiota induce and/or participate to food restriction in these patients and chronic constipation could induce and/or facilitate this change in gut microbiota. (2) The gut microbiota determines for each individual patient the type of PEM, i.e., marasmus type vs. kwashiorkor. In such case, manipulation of gut microbiota during AN (with antibiotics for example), might improve the issue of malnutrition during nutritional therapy.

MODEL 5: ANOREXIA NERVOSA AS A DYSIMMUNE DISORDER OF NEUROPEPTIDE SIGNALING

We review here recent evidence from experimental and clinical studies explaining how stressors could result in the dysregulation of eating behavior by the means of specific immunoglobulins (Igs) altering neuropeptide signaling (Figure 5). We also discuss a key role of intestinal bacteria and gut barrier dysfunction in this dysregulation. Although anorexia nervosa (AN) is classified as a psychiatric disease, the clinical observations that it involves multiple organ dysfunction, in addition to the core behavioral and psychiatric symptoms, underlines the need for an integrative pathophysiological approach. Anorexia is generally considered as the driving mechanism leading to malnutrition and its multiple organ consequences, leading in turn, to the perpetuation of anorexia and psychiatric comorbidity in a vicious circle. However, this classical approach does not clarify how anorexia and related symptoms may occur in so far healthy adolescents or adults. It is widely accepted that the risk of developing AN is markedly increased by different types of stressors: physical (such as puberty, trauma, abuse, or infections) and/or mental stress, including for example intellectual or physical exhaustion or repeated dieting (Hilbert et al., 2014). Familial history of stress events or stress-related disorders is another risk factor of

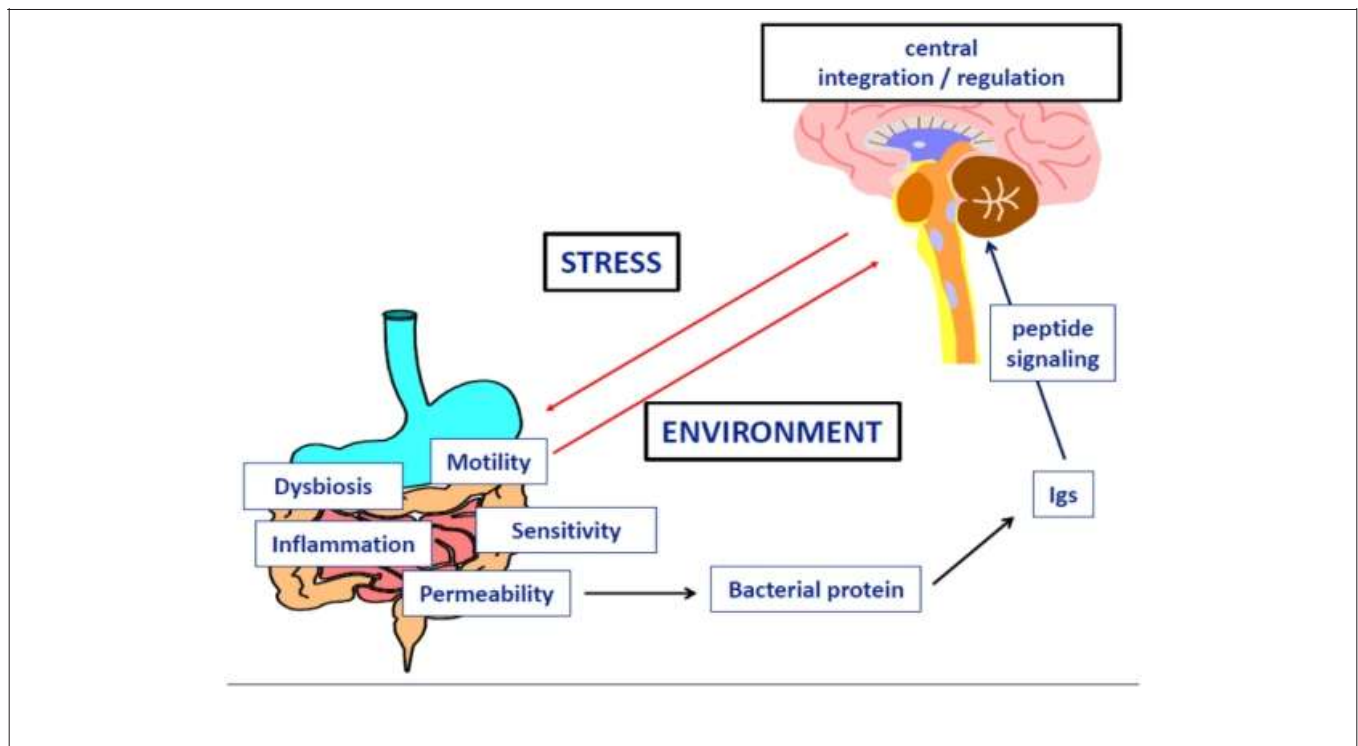


FIGURE 5 | Implication of microbial protein and specific Immunoglobulins in the dysfunction of neuropeptide signaling during anorexia nervosa.

AN, suggesting that genetic or epigenetic factors, so far poorly identified, may contribute to the maladjusted response to stress in patients developing AN (Trace et al., 2013). Finally, over the past 10–20 years, rapidly growing knowledge on the physiology of eating behavior identified neuropeptides and peptide hormones as major signaling molecules, in addition to monoamines, to regulate food intake, satiety, as well as pleasure and other behaviors and functions that may be altered during AN, e.g., sleep, anxiety, digestive motility, and sensitivity, endocrine functions and bone metabolism (Berthoud, 2011). This led to the concept of neuropeptide signaling dysfunction in AN (Inui, 2001), but an approach based only on peptide concentrations measurements and classical hormone-receptor interaction provided conflicting or paradoxical findings (Prince et al., 2009), e.g., that food intake remains low in anorectic patients despite increased orexigenic ghrelin (Otto et al., 2001) and decreased anorexigenic leptin (Hebebrand et al., 1995) levels.

We have performed a series of clinical and experimental studies indicating that neurobiological mechanisms of eating disorders and obesity may involve Igs reactive with peptide hormones regulating food intake and emotion, therefore also called peptide auto-antibodies (Fetissov et al., 2002). The initial finding was the identification of Igs in the serum of patients with AN or bulimia nervosa (BN) binding to α -melanocyte-stimulating hormone (α -MSH) in hypothalamic neurons (Fetissov et al., 2002). The clinical relevance of these Igs was further suggested by the correlation of their plasma levels and the Eating Disorder Inventory-2 (EDI-2) scores in AN and BN patients (Fetissov et al., 2005). To elucidate the potential origin of these Igs, an *in silico* search

was performed, based on the concept of molecular mimicry, with the hypothesis that some microorganisms present in the environment, especially in gut microflora, may present sequence homology with neuropeptides. This hypothesis was confirmed for several common microorganisms expressing in several proteins identical five consecutive amino acids with the main peptides involved in appetite, satiety, or emotion (e.g., α -MSH, ghrelin, leptin, orexin; Fetissov et al., 2008). In addition, both IgG and IgA classes of Igs reactive with peptide hormones were present in healthy subjects, further supporting a luminal source of antigens as well as physiological role of these Igs in the modulation of neuropeptide signaling. In support of this, other authors have shown the stimulatory effects of gut microbiota on all Igs classes in germ-free mice (Hansson et al., 2011).

With respect to AN pathophysiology, several of our studies focused on anti- α -MSH Igs, since this 13 amino acid peptide is a major regulator of energy balance, increasing satiety and energy expenditure via the activation of the melanocortin receptor type 4 (MC4-R), and is closely related to the hypothalamic response to stress (Cone, 2006). With this in mind, a study was undertaken in rodents showing the impact of chronic stressors on the levels and binding properties of anti- α -MSH Igs, related to food intake and anxiety-like behavior (Sinno et al., 2009). Furthermore, in a rat model of severe gut inflammation, inducing transient anorexia and major increase of intestinal permeability, deficient body weight gain persisted even after the resolution of intestinal inflammation and was associated with an increased level of anti- α -MSH Igs (Coquerel et al., 2012). We also adapted an animal model of AN called Activity-Based-Anorexia (ABA), combining a progressive reduction of time access to food coupled with

running wheel to mimic the hyperactivity of AN patients. We found that ABA mice were characterized by an increased colonic permeability which is favorable for the passage of antigens from gut bacteria to the host (Jésus et al., 2014).

To explore the implication of bacterial proteins from gut microflora in the occurrence of peptide-reactive Igs, we used a combined proteomic and immunological approach to identify α -MSH antigen-mimetic proteins in *Escherichia coli*. The commensal *E. coli* K12 was used because several *E. coli* proteins display five amino acids sequence homology with α -MSH (Fetissov et al., 2008). We identified ClpB, a heat-shock chaperone protein, as a conformational antigen mimetic of α -MSH (Tennoune et al., 2014). We showed that immunization of mice with ClpB induced the production of anti-ClpB Ig cross-reacting with α -MSH accompanied by altered food intake, body weight, anxiety and MC4-R signaling. Furthermore, mice receiving wild-type *E. coli* via intragastric gavage, decreased food intake and body weight gain and developed anti-ClpB-antibodies cross-reactive with α -MSH. In contrast, in mice receiving ClpB-deficient *E. coli*, food intake and Igs levels remained unaltered. Finally, plasma levels of anti-ClpB IgG cross-reactive with α -MSH were increased in patients with eating disorders, and several significant correlations were found between EDI-2 scores and anti-ClpB IgG and IgM levels in AN patients (Tennoune et al., 2014), similar to previous findings with anti- α -MSH reactive Igs (Fetissov et al., 2005). These data revealed that α -MSH-reactive Igs in humans and animals are generated mainly in response to bacterial ClpB protein produced by some gut bacteria including *E. coli*. It is of relevance to mention that the ClpB protein expression in bacteria is stimulated by various stressors preventing protein aggregation (Winkler et al., 2012), suggesting that ClpB could also be activated by host-induced starvation during a restrictive diet.

Altogether, these studies indicate that different stressors, including food restriction, via increased intestinal permeability, may favor bacterial protein translocation from the gut resulting in increased production of neuropeptide-reactive Igs. More specifically, bacterial protein ClpB may act as an anorexigenic α -MSH mimetic protein directly and indirectly via triggering production of Igs cross-reactive with α -MSH, and hence, altering the effects of this endogenous peptide hormone on satiety and anxiety. This may involve a modulatory role of Igs on α -MSH-induced activation of the MC4-R (Lucas et al., 2014), although the exact mechanisms need further investigation. Other groups have suggested that gut microbiota, especially *E. coli*, may influence the stress axis (Dinan and Cryan, 2012), while *E. coli* content was inversely related to the body mass index, including AN patients (Million et al., 2013). Studies on gut microbiota involvement in brain functions are discussed elsewhere (Cryan and Dinan, 2012); our data support a role of bacterial protein mimetics of peptide hormones in the gut-brain axis communication and validate the utility of proteomic approach as an efficient tool to detect such proteins.

In addition to the putative key role of α -MSH-mimetic protein and α -MSH-reactive Igs in AN pathophysiology, it is probable that other peptidergic systems involved in regulation of feeding and emotion can be altered via a similar mechanism

involving the gut-brain communications. Accordingly, the levels and properties of Igs reactive with ghrelin were altered in AN patients (Terashi et al., 2011), which might account with the previously proposed « ghrelin resistance » in these patients (Otto et al., 2001). In an opposite way, the affinity kinetics of ghrelin-reactive Igs in obese patients explained its increased orexigenic effects, through its reduced degradation (Takagi et al., 2014). Whether ghrelin-reactive Igs in AN patients may alter activation of the ghrelin receptor remains to be explored. Orexin-reactive Igs have been detected in narcolepsy (Deloumeau et al., 2010), which raises question about their possible implication in sleep disturbances during AN. It is worth underlining that several neuropeptides controlling food intake and anxiety, are also involved in gastrointestinal motor and sensitive regulation (e.g., ghrelin, CCK), which may explain the high prevalence of gastrointestinal symptoms during AN (Déchelotte et al., 2007).

In conclusion, we propose an integral pathophysiological scenario that fits to the natural history of AN with the following steps: (1) enhanced vulnerability to stress (genetic, epigenetic, or environmental factors); (2) major stressing events activating the stress-axis, increased intestinal permeability, and increased virulence of the microbiota; (3) bacterial proteins (e.g., ClpB) challenge the immune response and due to molecular mimicry, cause increased production of Igs cross-reactive with neuropeptides (e.g., α -MSH); (4) this results in altered food intake, anxiety, gastrointestinal discomfort and other consequences of altered central and peripheral melanocortin signaling; (5) global malnutrition and some specific macro- and micro-nutrient deficiencies contribute to the perpetuation of gut barrier and immune dysfunction as well as behavioral symptoms. This scheme opens potential therapeutic perspectives in AN, involving a multimodal approach including behavioral and/or pharmacological reduction of stress, restoration of gut barrier function, correction of microbiota imbalance, and specific targeting of bacterial proteins and/or related Igs.

MODEL 6: ANOREXIA NERVOSA TAKES ROOT IN THE PONDERO-NUTRITIONAL-EATING BASEMENTS DURING CHILDHOOD'S PREMORBID PERIOD

Physiological puberty process, partially genetically determined, is associated with strong physical, psycho-affective, hormonal, metabolic, and feeding behaviors variations. One possible hypothesis is that anorexia nervosa during adolescence is a kind of mismatch of this physiological process, permitted by underlying and premorbid vulnerability factors concerning the « pondero-nutritional-feeding » basements (**Figure 6**). Susceptibility factors existing during the premorbid period may concern development of taste, food choice, eating behaviors. The pubertal process stimuli interfering with these vulnerability factors could promote a failure of the « pondero-nutritional-feeding » system homeostasis resulting in later anorexia nervosa. The vulnerable system is a kind of trigger zone account for the symptom choice during difficult pubertal process

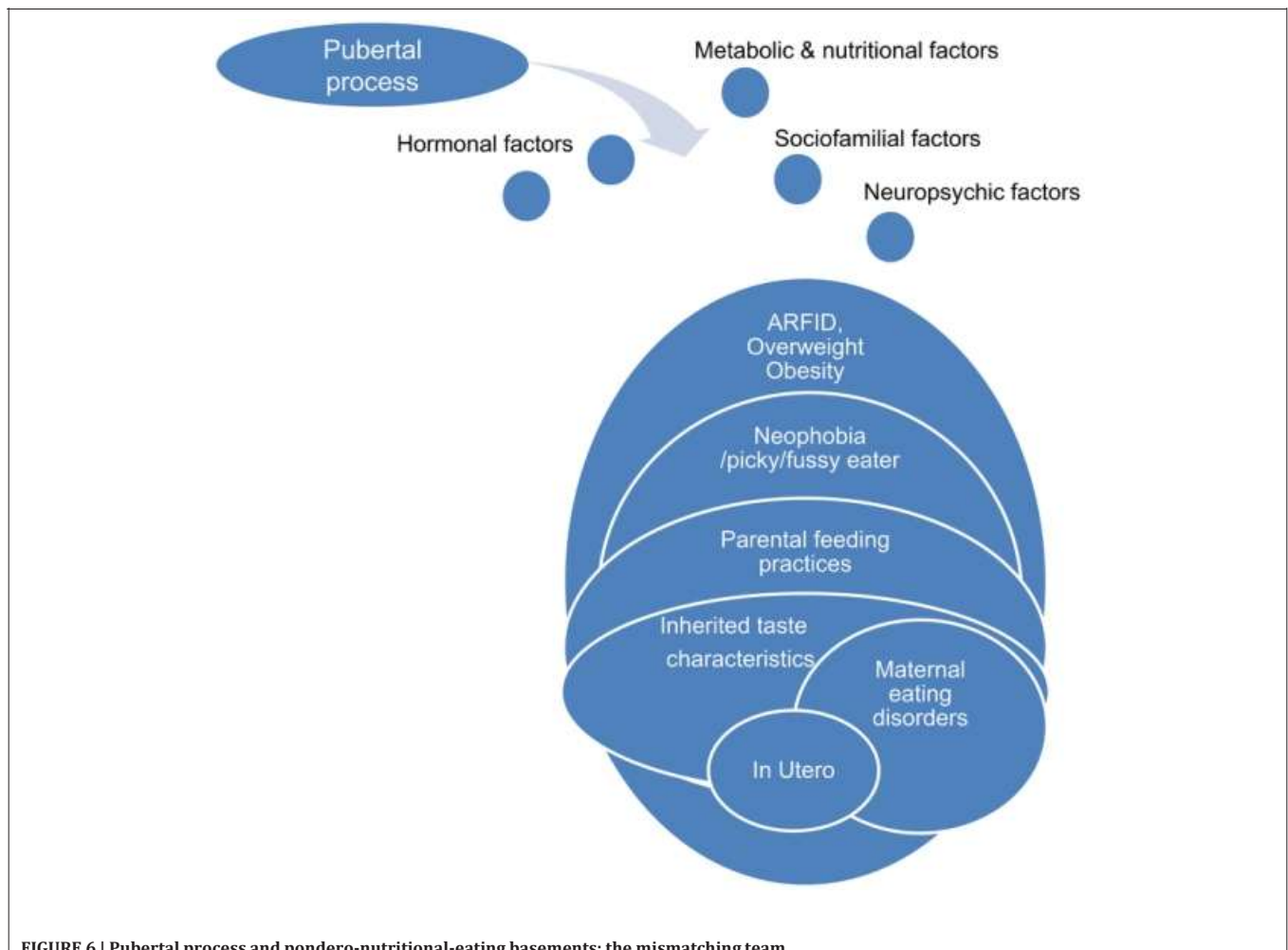


FIGURE 6 | Pubertal process and pondero-nutritional-eating basements: the mismatching team.

explaining how initial deviant eating behavior is becoming a severe psychosomatic disease, evolving for itself with denutrition and metabolic modifications promoting self-aggravation.

Development of Food Preferences

Development of food preferences and eating behaviors is a complex and paradoxical process starting probably in utero, involving inherited taste characteristic and interactions with environmental factors such as familial eating behavior, peers influence, and socio-cultural context (Birch, 1999).

Inherited Characteristics

Study of gusto-facial expression in 2 years old infants defines « hypoguesic », « normoguesic », and « hyperguesic » groups.

Hyperguesic group develops more difficulties in food choices and in maternal feeding interaction (Chiva, 1982). Individual genetic sensitivity to the bitter taste of phenylthiocarbamide (PTC) or 6-n-propylthiouracil (PROP) determines food preferences and dietary habits. Thirty percent of occidental population is “non-tasters” vs. 50% “tasters” and 20% called “super-tasters.” Such a marker for individual differences in taste perception could influence food preferences (bitter and foods rich in antioxidants,

sweetened and fat-containing foods, alcoholic beverages), and dietary behavior with subsequent links to body weight and chronic disease risk. There may be an inverse correlation between genetic sensitivity to PTC or PROP, BMI, and body fatness. The level of involvement of this phenotype mediated by the TAS2R38 gene in food regulation is still under debate. Other genetic bitter and non-bitter taste factors could play a role in food preferences including food aversion and deviant eating behaviors, such as the gustine gene which affects salivary ionic zinc concentrations—a trophic factor of taste buds (carbonic anhydrase VI). Otherwise, despite the fact that patients with anorexia nervosa often complain of disrupted smell and taste sense, there is no study concerning clinical population with eating disorders (Goldzak-Kunik et al., 2012).

Parental Feeding Practices and Sociocultural Influences

Children eating behavior is precociously influenced by sociocultural environment, parents feeding practices and particularly maternal eating habits and food preferences. Negative affects at mealtime, eating conflicts, struggles with food, and unpleasant meals in early childhood are associated

with higher risk for subsequent symptoms of anorexia nervosa. Maternal diet is one of the strongest predictor of childhood food consumption. Indeed, 15–20% of variation in children's difficulties could be associated with maternal feeding practices. A French study showed that extreme feeding practices as contingent, coercive or permissive style enhanced children's eating difficulties such as food neophobia, pickiness, low appetite, and low enjoyment in food. On the contrary, a flexible attitude, with repeated exposures to food, enhanced motivation to eat (Rigal et al., 2012). Parental excessive restriction and control of child feeding practices could limit the children eating autonomy and negatively influence their food choice, promoting inoppositereaction, consumption of "bad foods" including a diet rich in sugar, salt, and/or fat. Intrusiveness and other deleterious parental behavior, as not acknowledging the needs of the child, are also associated with higher risk of eating disorders (Gahagan, 2012).

Parental Eating Disorders

Several studies have shown that offspring of mothers with eating disorders are at higher risk of developing psychopathology in childhood and adolescence. Maternal eating disorders influence very early the quality of infant feeding, starting in utero with more frequent prematurity, low birth weight (which are themselves risk factors for eating disorders), overweight, and hyperphagia (Micali et al., 2011). Women with high weight and shape concerns breastfeed less their newborns, and might influence future children food choice because of their own food restrictions during this breastfeeding period. Later on, conflicts and unpleasant remarks at mealtimes, intrusive and control feeding practices may promote child negative eating behaviors, opposition attitude with food refusal, or infantile anorexia (Micali et al., 2009). Longitudinal study comparing children of women with eating disorders with "non-exposed" children showed modified feeding behaviors with more adhesion to "health conscious/vegetarian" dietary pattern in the first group, less fat and more carbohydrates in children of women with bulimia nervosa, and more high energy–dense foods in children of women with a history of binge sub-type anorexia. These modifications of food choice may be associated with a further risk of developing weight concerns, overweight, and eating disorders in later childhood and adolescence (Easter et al., 2013).

Premorbid Overweight or Obesity

There is no study concerning association between overweight or obesity in childhood and further episode of anorexia nervosa in adolescence. However, overweight or obesity in childhood are strongly associated with hyperphagia, even though incidence of other types of eating disorders is unknown. Even if anorexia nervosa and binge eating disorder differed on premorbid personality/behavioral problems, and family overeating, risk factors for bulimia nervosa are mainly shared with anorexia nervosa and binge eating. Premorbid BMI is positively correlated to binge eating disorders and bulimia nervosa during the course of anorexia nervosa episode (Nishumira et al., 2008). Overweight or obesity during pre-morbid period is more frequent in male adolescent with anorexia nervosa (30–40%). Otherwise, recent studies suggest that adolescents with a history of premorbid

overweight or obesity may develop restrictive eating disorders, with severe weight loss, severe medical complications, and a poorer prognosis.

Food Neophobia/Pickiness/ARFID

Even though studies do not provide firm conclusions concerning which problems are predictive, the presence of eating problems in early childhood or an eating disorder in adolescence confers a strong risk for an eating disorder in young adulthood (Kotler et al., 2001). Digestive troubles in neonatal period or in early infancy (severe gastro oesophageal reflux) or food aversions secondary to gastrointestinal disease with nausea and vomiting have been reported to have negative consequences on appetite and eating patterns. Food neophobia is a survival mechanism with rejection of unknown foods while picky/fussy eating, a frequent problem in childhood (8–50%). It is defined as a rejection of familiar food with consumption of an inadequate variety of food, and low intakes of vegetables, and fruits. Risk factors for a later development of eating disorders include picky eating and digestive problems with a significant stability over the 10-year span studied, beginning at ages 1–10 (Marchi and Cohen, 1990). Even if food neophobia and picky eating are two distinct entities, there is probably an overlap and both may be associated with a certain type of eating disorders. ARFID (Avoidant/Restrictive Food Intake Disorder in Children and Adolescents) is a new category of DSM-5 classification, including those with selective (picky) eating since early childhood. Common eating-specific behaviors and symptoms in the ARFID group contain food avoidance, loss of appetite, abdominal pain, and fear of vomiting. Patients with ARFID are younger than those with AN, more likely to present before age 12, and more likely to be male (Norris et al., 2014). In a recent study, patients with ARFID were significantly underweight with a longer duration of illness, more likely to have comorbid medical conditions, anxiety or mood disorder. The course of ARFID is unknown but it is possible that these children and adolescents would develop other types of eating disorder such as AN, BN, or EDNOS (Fisher et al., 2014).

Conclusion

Anorexia nervosa takes root in vulnerability factors determining childhood feeding and eating behaviors bases. These susceptibility factors, including food preferences, inherited taste factors, environmental factors, and early inadequate food intakes may be impacted by modifications associated to the pubertal process, therefore untitled the "mismatching team." Detection of particular traits of eating patterns or deviant ponderal history may indicate vulnerability and high risk for some toddlers or children to develop anorexia nervosa in adolescence.

MODEL 7: ANOREXIA NERVOSA (AN) IS AN ATTEMPT TO PRESERVE MENTAL HOMEOSTASIS

AN can be considered as the result of an attempt to restore mental homeostasis that uses the bodily domain by way of restricted

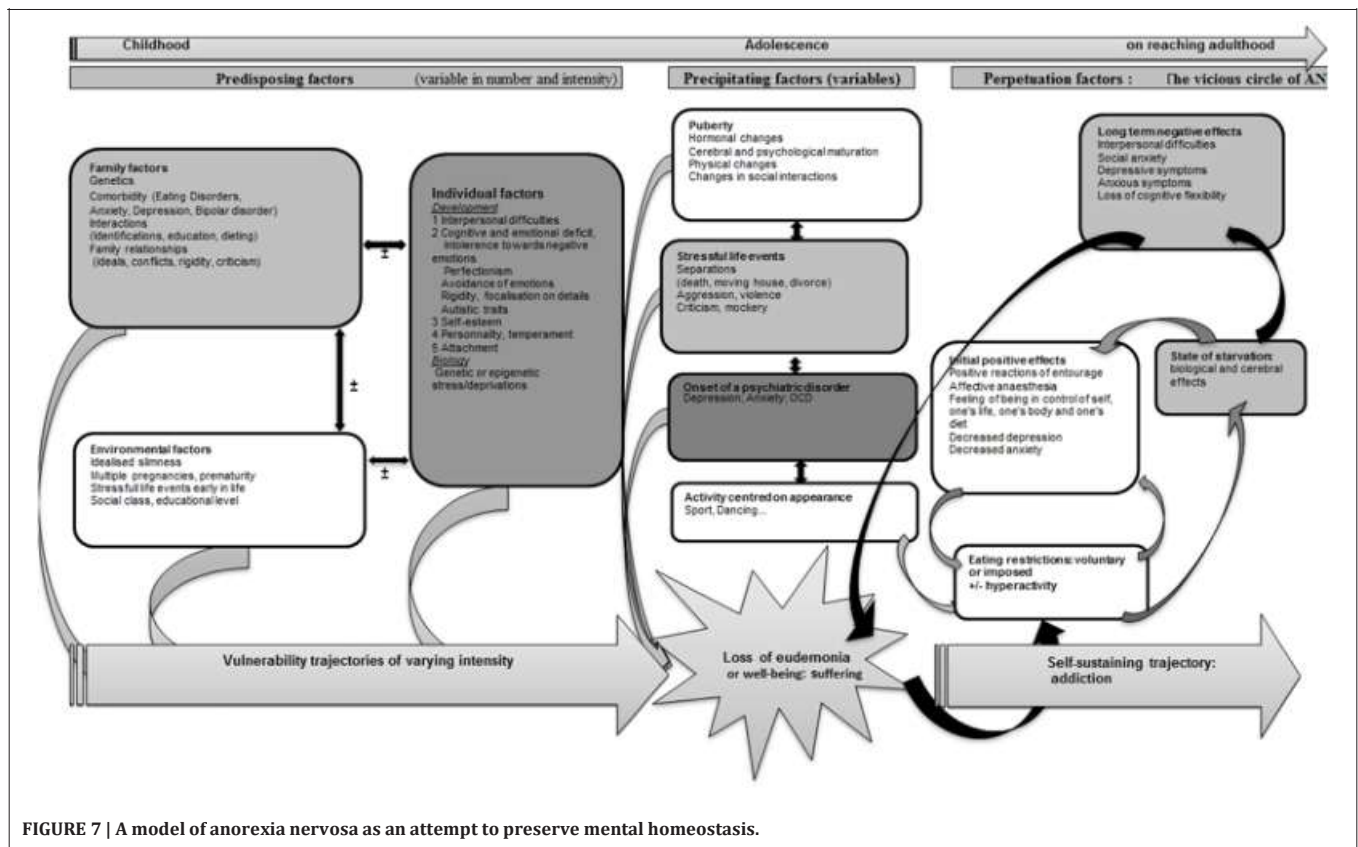


FIGURE 7 | A model of anorexia nervosa as an attempt to preserve mental homeostasis.

eating (Figure 7). Certain subjects, because of predisposing factors (Garner et al., 1993) could develop trajectories of vulnerability toward AN. This vulnerability could come to the surface on the occasion of precipitating elements leading to the loss of “well-being” or “eudemonia” as a result of individual factors (mental or somatic) or interpersonal factors (See diagram). The unsettled homeostasis, in a first stage, is restored by restricted eating, a process that could contribute to prolonging AN. Vulnerability trajectories and precipitating factors are liable to vary in nature and intensity from one subject to another, and would explain the variable clinical expressions in terms of age at onset, clinical symptoms, intensity of the disorder, duration of evolution, therapeutic response, or evolution to chronic illness, bulimia or other psychiatric disorders.

The predisposing elements contributing to an AN vulnerability trajectory are not all present at once in patients, as they assemble to form trajectories made up of numerous different vulnerability factors. These predisposing elements include (1) family factors, including genetic susceptibility to the disorder (Pinheiro et al., 2010; Trace et al., 2013), a psychiatric family history of eating disorders (Strober et al., 2000), anxious, depressive, or bipolar disorders (Bould et al., 2015), traits such as perfectionism or rigidity (Treasure et al., 2010), disturbed family interactions early in life (deprivation, violence—Jaite et al., 2012) or family interactions connected with eating habits (Hill and Franklin, 1998; Haycraft et al., 2014; Loth et al., 2014; Micali et al., 2014). Some (2) individual factors might also be

involved, such as female gender (Connan et al., 2003), early exposure to stress, including intra-uterine stress (Connan et al., 2003; Treasure et al., 2010) via epigenetic regulation (Toyokawa et al., 2012) and disrupted personal development evidencing itself in affects, cognitions and interpersonal relationships (Connan et al., 2003). Depending on the concepts mobilized in different studies, these phenomena are evidenced in the form of personality disorders or dimensions (perfectionism, obsessive-compulsiveness, neuroticism, negative emotionality, harm avoidance, low self-directedness, low cooperativeness, low novelty seeking, and traits associated with avoidant personality disorders) (Cassin and Von Ranson, 2005), attachment disorders (Tasca and Balfour, 2014), emotional regulation disorders (Haynos and Fruzzetti, 2011), cognitive disorders (weak central control, rigidity) (Treasure and Schmidt, 2013), anxiety disorders (Raney et al., 2008; Touchette et al., 2011), and biological or genetic particularities (see for example Bailer and Kaye, 2011; Tremolizzo et al., 2014). (3) Environmental factors also play an important role, including stressful life events such as prematurity (Favaro et al., 2006), multiple birth (Raevuori et al., 2014), and social factors such as the ideal of slimness in society (Garner, 1993), social class (Godart et al., 2013), and educational level (Goodman et al., 2014).

The trajectories derived from these various elements remain to be characterized. They could roughly correspond to five types, dominated respectively by (1) obsessiveness and perfectionism, (2) major interpersonal difficulties verging on Asperger’s

syndrome, (3) anxiety, (4) mood disorders, recurrent unipolar depression, bipolar disorders, and (5) personality disorders interwoven with deprivation or violence in the early years.

The precipitating elements are mainly stressful life events (Connan et al., 2006; Schmidt and Treasure, 2006) or negative emotional states (Fox and Power, 2009), sometime in a setting of incipient psychiatric comorbidity (depression, anxiety, OCD, Godart et al., 2002, 2007), or most often associated with puberty and including hormonal factors (Klump, 2013) or psychological, physical, and relational factors.

The start of eating restrictions appears in various contexts: (1) the psychological dissatisfaction linked to a negative emotional state (poor self-esteem) is transferred to the body (Fox and Power, 2009) and triggers a will to restrict food intake linked to dissatisfaction with the body, (2) a slimming diet (as a result of weight gain, family pressures, peer group influence), (3) an intercurrent event—operation involving the digestive tract, (4) emotional state (via stress—Greeno and Wing, 1996—anxiety or depression) or a somatic pathology can trigger anorexia in its prime meaning (loss of appetite). However, whatever the previous vulnerability trajectory or the precipitating events, these subjects discover the positive effects of food intake restrictions (as has been described in the short term in depression, Fond et al., 2013), enabling a temporary return to eudemonia. This wellbeing is the result of biological modifications that may be caused by starvation, the decrease in anxious and depressive symptoms (Kaye et al., 2003), the feeling of having control over one's life, one's body, and one's diet, the sometimes positive feedback from the entourage, and in some cases affective anesthesia (Garner, 1993; Fox and Power, 2009).

In all cases, however, the balance obtained is fragile and short-lived, since the causes of the imbalance persist. Further to this, the lack of food (often compounded by hyperactivity), because it has biological and hormonal consequences, (leads to anxious and depressive symptoms Swenne and Rosling, 2010; Gauthier et al., 2014), interpersonal difficulties (Treasure and Schmidt, 2013), social anxiety (Coulon et al., 2009), and parental criticism linked to the patient's state (Treasure and Schmidt, 2013; Duclos et al., 2014) with which the subject tries to cope by the same means of food intake restriction, even intensifying food deprivation, in order to regain the same effect, which encloses the subject in the vicious circle of AN. In this model, AN can be considered as an addictive behavior in which the object of the addiction is the control exercised over one-self and one's hunger (Jeammet, 1991; Venisse, 1991; Goodman, 2008; Duclos et al., 2014).

The clinical profile observed by clinicians is composite, and depends on elements linked to the vulnerability trajectory (for example one of the five previously mentioned), to age at onset of the disorder (for instance pre-pubertal subjects exhibit growth and pubertal delay), adolescents are less often in denial of their thinness than adults (Couturier and Lock, 2006). It also depends on precipitating factors (for example if a depressive state precedes the disorder, suicidal ideas or psychomotor retardation can be present) and on the intensity and duration of food deprivation. We hypothesize that the severity of the AN evolution trajectory is also linked to the severity of vulnerability factors, to the intensity

of the state of starvation and to AN prognosis: the more severe the difficulties experienced before AN onset, the more likely is the disorder to be severe and become chronic, and the greater are the mental disturbances compounding AN.

We propose a global, integrative clinical model of Anorexia Nervosa (AN), starting from models developed previously (Garner, 1993; Connan et al., 2003; Fairburn and Harrison, 2003; Schmidt and Treasure, 2006; Fox and Power, 2009; Herpertz-Dahlmann et al., 2011; Tasca et al., 2013; Treasure and Schmidt, 2013; Treasure et al., 2014) and from the concept of mental homeostasis, which postulates (Agnati et al., 2011) (1) that the concept of biological homeostasis can be transposed to the mental domain, (2) that any individual, from a psychological viewpoint, possesses a state of equilibrium called “the well-being of the human psyche” or “eudemonia,” and (3) that mental homeostasis sustains eudemonia by enabling a person to feel at ease with him/herself (emotionally and bodily) and with others (interpersonal relationships). Any event in one or other of these areas (emotional, bodily, interpersonal) that upsets this mental homeostasis will generate a state of “mental allostasis,” which is painful for the subject, who will struggle against it by way of adaptive processes to restore the earlier equilibrium. A person's mental homeostatic equilibrium is a dynamic balancing process that is variably vulnerable, depending on a developmental trajectory that is linked to family, individual and environmental factors.

CONCLUSIONS

Just as for many of complex disorders, scientific evidences can lead to different heuristic models in AN. An efficient model should use validated risk factors to further define the potentially involved mechanisms of actions of anorexia nervosa. The predisposing elements contributing (see Model 7) to AN include (1) presence of a psychiatric family history of eating disorders, (2) presence of personal anxious, depressive or bipolar disorder, (3) different personality traits such as perfectionism or rigidity, (4) disturbed family interaction early in life (deprivation and violence), (5) family interactions connected with eating habits, but also (6) female gender, (7) early exposure to stress, including intra-uterine stress, multiple birth and prematurity, and (8) disrupted personal development. Social factors also have a role, such as (9) the ideal of slimness in society, (10) social class, and (11) educational level.

One of the specificity of anorexia is the presence of excessive physical exercises even though there is food deprivation or purging behaviors in underweight patients. An abnormality of the rewarding value in AN of food and exercise has thus been proposed as a core feature, which is supported by the role of endogenous opioids and dopamine pathways in the reward properties of food (see Model 1), and indirectly by an excess of specific polymorphisms of the genes coding for opioid and dopamine receptors or transporters in AN. An abnormal reward process could potentially involve more specifically a preference for delayed reward and/or reduced capacity to (as in controls) favor immediate reward. Such preference for delayed reward does give sense to avoid food

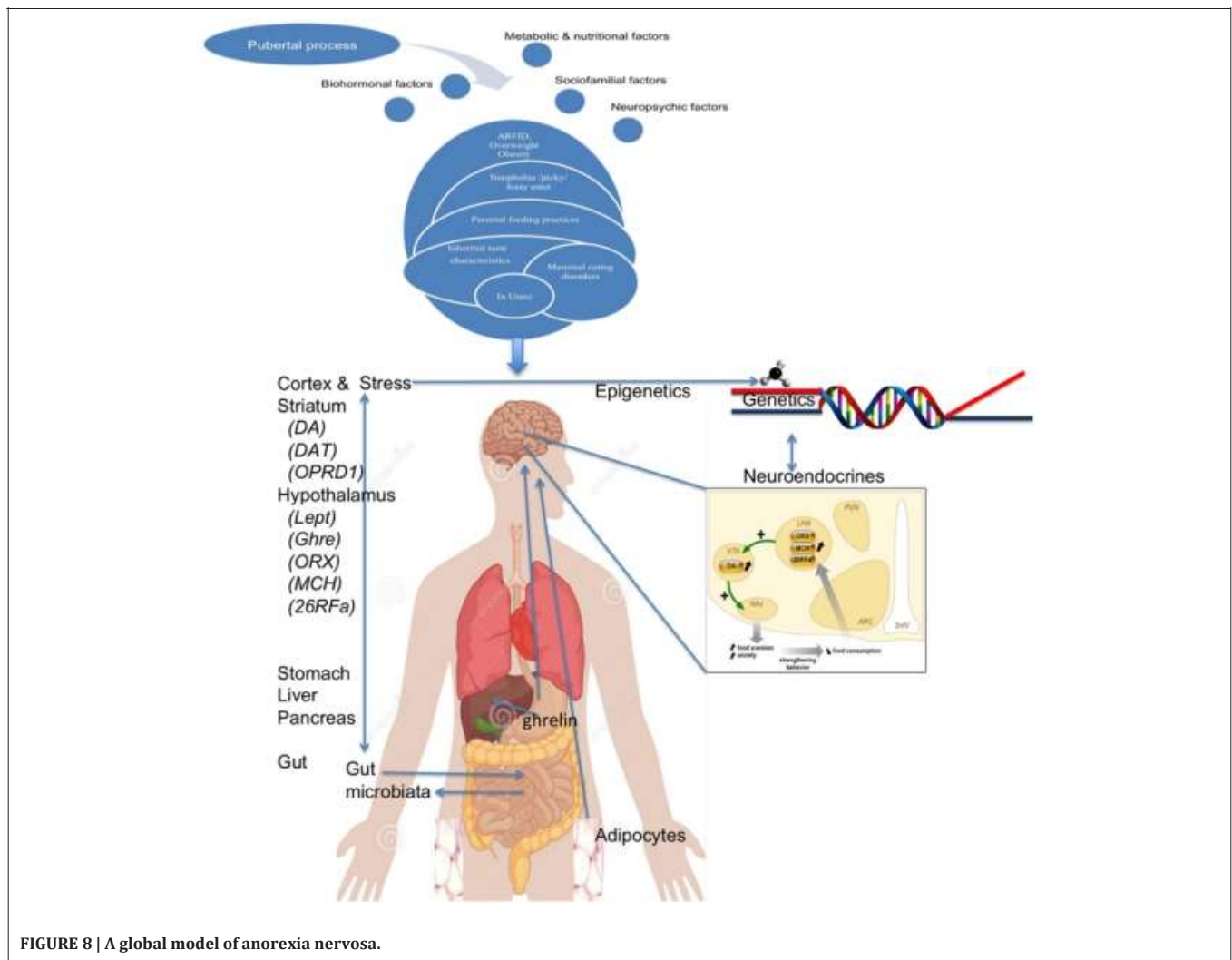


FIGURE 8 | A global model of anorexia nervosa.

(in order to lose weight) while starving, and not resting (while exhausted). Amphetamine-induced dopamine release indeed increased anxiety in individuals recovered from AN potentially explaining why food-related dopamine release might generate anxiety in AN patients vs. pleasure in healthy subjects (see Model 2). Recent evidence for a (marginal) role of a calcineurin gene derived from the largest GWAS performed up to now, support this view, as this gene independently explains part of human variations in endurance exercise capacity and tolerance (He et al., 2010a). Proposing that an abnormal reward process is central in AN is supported by the fact that plasma levels of ghrelin- an orexigenic hormone which usually induces food-motivated behavior- is increased in AN. As Ghrelin exerts pleiotropic effects, for example through heterodimers, including the modulation of the dopaminergic reward system, its role in AN is possible, and indeed supported by some genetic studies. But the neurons from the LHA send projections to the brain reward circuitry also contain other factors apart from Ghrelin such as the expressing orexins, MCH, and 26RFa (see Model 3). Orexin neurons in the LHA is for example strongly linked to preferences for cues associated with drug and food reward,

and orexin injected into the VTA increases dopamine release in the accumbens nucleus (NAc). Even though the role of the MCH system has never been investigated in AN, it is interesting to note that the orexigenic effect of MCH is largely dependent upon its action in the NAc. 26RFa levels were also abnormal in patients with restrictive AN, as significantly increased all over the day compared to healthy subjects, and mapping of GPR103 mRNA (the receptor of 26RFa) in the brain revealed that the 26RFa receptor is also expressed in the VTA and the NAc. The orexigenic neuropeptides including ghrelin, orexins, and 26RFa are therefore clearly up-regulated in AN their orexigenic profile potentially reflecting an adaptive mechanism to promote food intake, trying –inefficiently- to counteract undernutrition, and potentially reinforcing dopamine-induced anxiety in the reward system of AN patients, and thus aversion to food.

The gut microbiome contributes to the risk and pathogenesis of malnutrition through nutrient metabolism and immune function, but has also shown specificities in patients with AN, such as a deviation of microbiota, and an increase of *M. smithii* (see Model 4) which are directly involved in energy efficiency. It is thus possible that some pre-existing changes in

gut microbiota induce and/or participate to food restriction, for example through the frequently associated chronic constipation observed in AN. Even more precisely, some authors propose that food restriction, via increased intestinal permeability, may favor bacterial protein translocation from the gut, resulting in increased production of neuropeptide-reactive Igs, the bacterial heat-shock chaperone protein (ClpB) potentially acting as an anorexigenic α -MSH mimetic protein. As the levels and properties of Igs reactive with ghrelin were also altered in patients with AN (see Model 5), antigens could involve other neuropeptides.

Apart from the inheritance of genetic polymorphisms from parents to children, risk factors may also get from a generation to the other through parents/child interactions. Indeed, women with high weight, and shape concerns, breastfeed less their newborns (see Model 6). Later on, conflictive, intrusive and excessive controls of feeding practices promote child negative eating behaviors (references). Longitudinal study also showed that women with eating disorders are more frequently adopting “health conscious/vegetarian” dietary pattern. Furthermore, eating disorder in adolescence, such as food neophobia, pickiness, or ARFID (Avoidant/Restrictive Food Intake Disorder in Children and Adolescents) confers a strong risk for an eating disorder in young adulthood.

All together (**Figure 8**), we could propose that subjects genetically at risk and/or exposed to pathological feeding attitudes by their parents, may have early non-specific eating disorders that are usually unnoticed, such as traits related to food neophobia, pickiness or ARFID. In relation to other risk factors, such as subthreshold difficulties could worsen in some patients (for example because of personal or familial psychiatric morbidity, perfectionism or rigidity traits or rigidity), and even develop anorexia nervosa when meeting triggering

factors (such as stress around puberty), in a facilitating environment (wealth of food and high value of thinness). Throughout such pathway, food would progressively change its rewarding value, losing the positive value of satiety, or increased the positive feelings associated with weight loss or excessive exercise, potentially through an increased preference for delayed reward. Interestingly, such progression of the disease could be explained by the accumulation of risk factors (occurring at different times of life), but also by gene \times gene interaction (two-hit hypothesis), epigenetic modifications (throughout a gene–environment interaction), and even via increased intestinal permeability which may lead to increased production of neuropeptide-reactive immunoglobulins. Even if some aspects are still speculative, they lead to two important conclusions. Firstly, many aspects developed herein are still very preliminary in anorexia nervosa, and could be much more important than initially thought (such as microbiota, epigenetic regulations, and immunity) when studied with more patients and more powerful technics. Secondly, proposing an integrative model of AN reinforces the idea that depicting the mechanisms of the disorder will need to study those different aspects together, all singular approaches would decrease the chances to cover all aspects of this complex disorder.

AUTHOR CONTRIBUTIONS

JE wrote the introduction and conclusion with PG and reviewed the different parts of the article and figures. PG wrote the introduction and conclusion with JE and reviewed the different parts of the article and figures. CB, NC, JD, PD, MH, SF, NG, JM, NR, CR, VT, and OV participated in writing the article and designing of figures.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer VP declared a shared affiliation and previous co-authorship with author OV to the handling Editor, who ensured that the process nevertheless met the standards of a fair and objective review.

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ARTICLE 2

Une OVERVIEW TRANSDISCIPLINAIRE des MÉTA-ANALYSES et des REVUES SYSTÉMATIQUES sur les TRAITEMENTS MÉDICAMENTEUX de L'ANOREXIE MENTALE

Le second article est une overview transdisciplinaire sur les traitements médicamenteux de l'anorexie mentale. Il a été publié en Février 2019 dans la revue *Journal of Clinical Medicine* (revue indexée dans Medline, Impact Factor 2019 : 5.688).

Si les troubles des conduites alimentaires survenant à l'adolescence cumulent les paradoxes (Jeammet, 2010), la place des traitements médicamenteux n'en n'ai pas le moindre. Alors que dans les représentations de la plupart des cliniciens "aucun médicament ne soigne l'anorexie", les guidelines internationaux nous mettent en garde quant à leur utilisation exclusive : "Do not offer medication as the sole treatment for anorexia nervosa" (chap1.3.24) (National Institute for Health and Care Excellence, 2017). Les prescriptions médicamenteuses sont néanmoins extrêmement répandues dans les prises en charge des différents symptômes associés aux TCA, le plus souvent basées sur des cultures d'équipe ou des expériences personnelles dans le cadre disciplinaire de chacun. Les données de la littérature sur ce sujet concernent des champs disciplinaires restreints, et restent le plus souvent peu accessibles aux professionnels extérieurs à la spécialité concernée.

Cet article a pour objectif de faire un état des lieux des connaissances actuelles sur les traitements utilisés pour l'anorexie mentale dans les domaines de la psychiatrie, de la médecine somatique ou de la nutrition et d'ouvrir une réflexion transdisciplinaire sur les perspectives thérapeutiques. Ce travail est né de collaborations multiples incluant psychiatres et pédopsychiatres, nutritionnistes, endocrinologues et endocrinologues

pédiatriques, tous membres du réseau national transdisciplinaire, la Fédération Française Anorexie Boulimie (FFAB). Il a été rédigé et co-cordonné par l'auteure et une psychiatre, et la discussion a été co-construite dans une approche intégrative.




Ce travail a utilisé une méthodologie rigoureuse qui répond aux exigences recommandées pour les overviews systématiques (Pollock, Campbell, Brunton, Hunt, & Estcourt, 2017 ; Ballard, & Montgomery, 2017). Il a nécessité de multiples interactions et échanges avec les acteurs des différentes sous-disciplines en intra-disciplinaire, mais également entre champs disciplinaires distincts. Si les résultats evidence-based concernant l'utilisation de ces nombreux traitements sont limités, ce travail original est le premier à fournir une vision intégrative et actualisée de tous les traitements disponibles dans les diverses disciplines concernées par la prise en charge complexe de ces patients. Nos résultats sont limités notamment pour des raisons d'hétérogénéité méthodologique des études incluses, et l'accent est mis sur la nécessité, pour les futures études, d'une méthodologie transdisciplinaire visant à optimiser les critères d'inclusion, les objectifs et le champ de ces études. L'approche transdisciplinaire paraît particulièrement utile pour penser et améliorer le phénotypage des patients inclus dans les études. Elle devrait permettre d'optimiser les critères évaluant l'efficacité synergique d'une utilisation conjointe des traitements somatiques, nutritionnels et psychiatriques, particulièrement pour les formes sévères et résistantes d'anorexie mentale. Cet article participe à établir une culture commune transdisciplinaire par la mise en commun de connaissances et d'outils destinées aux prescripteurs directement impliqués auprès des patients souffrant de TCA mais plus largement est destinée aux différents protagonistes du champ TCA.

Cet article fera l'objet d'une communication orale à l'Eating Disorders International Conference (EDIC) (Glasgow en Mars 2020. N.Godart, C.Blanchet).



Review

Medication in AN: A Multidisciplinary Overview of Meta-Analyses and Systematic Reviews

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Received: 15 January 2019; Accepted: 20 February 2019; Published: 25 February 2019

Abstract: Drugs are widely prescribed for anorexia nervosa in the nutritional, somatic, and psychiatric fields. There is no systematic overview in the literature, which simultaneously covers all these types of medication. The main aims of this paper are (1) to offer clinicians an overview of the evidence-based data in the literature concerning the medication (psychotropic drugs and medication for somatic and nutritional complications) in the field of anorexia nervosa since the 1960s, (2) to draw practical conclusions for everyday practise and future research. Searches were performed on three online databases, namely MEDLINE, Epistemonikos and Web of Science. Papers published between September 2011 and January 2019 were considered. Evidence-based data were identified from meta-analyses, if there were none, from systematic reviews, and otherwise from trials (randomized or if not open-label studies). Evidence-based results are scarce. No psychotropic medication has proved efficacious in terms of weight gain, and there is only weak data suggesting it can alleviate certain psychiatric symptoms. Concerning nutritional and somatic conditions, while there is no specific, approved medication, it seems essential not to neglect the interest of innovative therapeutic strategies to treat multi-organic comorbidities. In the final section we discuss how to use these medications in the overall approach to the treatment of anorexia nervosa.

Keywords: anorexia nervosa; drug-treatment; pharmacotherapy; medication; nutrition; comorbidity; complication

1. Introduction

Anorexia nervosa (AN) is a severe condition with high morbidity and mortality rates resulting from both somatic and psychiatric aspects of the disorder [1]. International guidelines recommend treatment based on a multidisciplinary approach, including nutritional, somatic, psychiatric, and social aspects [2–5]. This global treatment is mainly based on nutritional and psychotherapeutic approaches associated with the treatment of medical and socio-familial complications. In the National Institute for Health and Care Excellence (NICE) guidelines [4] it is clearly mentioned that medications cannot be seen as the sole treatment for anorexia nervosa (Number 1.3.24 see Table 1).

As stated by Aigner et al. [6] the treatment objectives in AN include weight gain, prevention of weight loss, a change in eating behaviours, reduction of associated psychopathologies (e.g., preoccupations with body image, depression, anxiety, obsessive compulsive symptoms) and the treatment of associated medical conditions (e.g., disturbances of the gonadal axis, infertility, osteoporosis). Medication for its part is used to treat AN symptoms including eating disorder symptoms (eating attitudes, refusal to gain weight, preoccupation about shape and weight, obsessions about food ...) and psychiatric symptoms (depression, anxiety, obsessions, and compulsions.). In addition, AN patients frequently have severe malnutrition and medical complications that can be treated by medication. Indeed, while the return to a normal weight by re-feeding associated with multidisciplinary care is crucial and enables the correction of many somatic functional disorders, it seems essential not to neglect the usefulness of somatic medication in limiting the short and long-term physical complications, optimizing quality of life and promoting a favourable outcome in all fields affected by AN (somatic, psychiatric and social).

In 2011 the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders [6] concluded that the majority of the drugs to treat AN are used off-label [6]. These drugs are widely prescribed, but not in compliance with international guidelines [7,8], and can therefore be potentially unsafe for patients with AN.

For everyday practice, clinicians need improved recommendations about what medications can be used, for what purpose and in which conditions. Current guidelines give some indications for the use of different medications, but they lack precision and do not define who can be treated, when, and with which medication (as seen in Table 1, NICE recommendations for medication in AN). When

clinicians try to find information in the literature, it is not easy, as there are numerous publications on the subject. For example, since the WFSBP guidelines were established for the pharmacological treatment of eating disorders, there have been around 300 reports on the topic of medication and AN, and no review covering all drugs used in the nutritional, somatic, and psychiatric fields.

The main aim of this work is to offer clinicians a multidisciplinary overview of the evidence-based published literature concerning drug treatments in the field of AN. This overview is based on the conclusions of meta-analyses, failing that on systematic reviews, and otherwise on trials (randomized or if not open-label studies). Unlike other reviews, this one is not restricted to drugs used to treat AN symptoms or psychiatric symptoms, but also includes the treatment of the medical conditions and the nutritional aspects associated with AN.

Table 1. Extract from the National Institute for Health and Care Excellence (NICE) recommendations [4] for medication in anorexia nervosa (chapter 1.3) and eating disorders in general including anorexia nervosa (chapter 1.8).

Recommendations

Medication for anorexia nervosa

1.3.24 Do not offer medication as the sole treatment for anorexia nervosa.

Dietary advice for people with anorexia nervosa [...]

1.3.21 Encourage people with anorexia nervosa to take an age-appropriate oral multi-vitamin and multi-mineral supplement until their diet includes enough to meet their dietary reference values.

Comorbid mental health problems

1.8.12 When deciding in which order to treat an eating disorder and a comorbid mental health condition (in parallel, as part of the same treatment plan or one after the other), take the following into account:

- The severity and complexity of the eating disorder and comorbidity.
- The person's level of functioning.
- The preferences of the person with the eating disorder and (if appropriate) those of their family members or carers.

1.8.13 Refer to the NICE guidelines on specific mental health problems for further guidance on treatment.

Medication risk management

1.8.14 When prescribing medication for people with an eating disorder, and comorbid mental or physical health conditions, take into account the impact that malnutrition and compensatory behaviours can have on medication effectiveness and the risk of side effects.

1.8.15 When prescribing for people with an eating disorder and comorbidity assess how the eating disorder will affect medication adherence (for example, for medication that can affect body weight).

1.8.16 When prescribing for people with an eating disorder, take into account the risks of medication that can compromise physical health due to pre-existing medical complications.

1.8.17 Offer electrocardiogram (ECG) monitoring for people with an eating disorder who are taking medication that could compromise cardiac functioning (including medication that could cause electrolyte imbalance, bradycardia below 40 beats per minute, hypokalaemia, or a prolonged QT interval).

Substance or medication misuse

1.8.18 For people with an eating disorder, who are misusing substances, or over-the-counter or prescribed medication, provide treatment for the eating disorder unless the substance misuse is interfering with this treatment.

1.8.19 If substance misuse or medication is interfering with treatment, consider a multidisciplinary approach with substance misuse services.

Growth and development

1.8.20 Seek specialist paediatric or endocrinology advice for delayed physical development or faltering growth in children and young people with an eating disorder.

2. Methods

A systematic literature search was performed on the topic of medication in AN in order to perform a systematic overview, according to the following method.

2.1. Data Sources and Search Strategies

Searches were performed on online databases, namely MEDLINE, Epistemonikos and Web of Science. Inclusion and exclusion criteria are described in Table 2.

Table 2. Inclusion and exclusion criteria for the systematic overview of systematic reviews, meta-analyses and selected trials (Population Intervention Control Outcome and Study design (PICOS) criteria and other elements).

Parameters	Inclusion Criteria	Exclusion Criteria
Patients	- AN 1 (with or without the mention of the restrictive or binge/purging types) - Human studies - All ages	- BN 2, BED 3, other ED 4 - Mixed eating disorder samples (AN and any other ED)
Interventions	- Medication for AN (psychotropic or somatic or nutritional)	- Medication for refeeding complications
Comparators	- All comparison groups (placebo or active drug or treatment as usual)	
Outcomes	- All criteria linked to ED symptoms, psychiatric and somatic symptoms, and nutritional aspects, as appropriate	
Study design	- Meta-analyses and systematic reviews with a detailed methodology, including RCTs 5 and/or open trials	- Narrative or qualitative reviews - Overviews - Reviews of unpublished data
Period considered	- Papers published between September 2011 (since the publication of The World Federation of Societies of Biological Psychiatry Guidelines for the Pharmacological Treatment of Eating Disorders) [6] and 30th January 2019	
Language	- English and French	

1 AN: Anorexia Nervosa; 2 BN: Bulimia Nervosa; 3 BED: Binge Eating Disorders; 4 ED: Eating Disorder; 5 RCT: Randomized Controlled Trial.

Only meta-analyses and systematic reviews with a detailed methodology were retained; narrative or qualitative reviews were excluded, as they provide elements only on some studies, and can be biased by a lack of information. We excluded studies that investigated mixed eating disorder groups, as their conclusions cannot be extended to AN.

The searches were complemented by a manual search: reference lists of articles were manually investigated to identify reviews or meta-analyses potentially relevant for inclusion that were not detected by electronic search.

The search strategies were conducted in two phases by two of the investigators (C.B., N.G.).

First, we defined a search in order to identify all reviews and meta-analyses published on the topic of drug treatments in AN with the following terms and algorithm, which, among the algorithms tested with different key words and combinations, proved to be the one that retrieved the largest corpus of papers: “anorexia nervosa and pharmacotherapy or drug treatment or medication or nutrition or enteral nutrition or weight restoration”.

The search on the three databases previously mentioned selected 289 papers, 45 of which were reviews or meta-analyses on the topic (see Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart Figure 1). Two further papers were identified by manual research.

Among the 45 reviews or meta-analyses, 26 were excluded for the following reasons: 16 were overviews and/or not systematic reviews with no explicit methodology for the selection of the papers mentioned [9–24], one review [25] predated the World Federation of Societies of Biological Psychiatry review, one [26] reviewed the same eight studies as a meta-analysis included [27], five focused on unpublished data, or studies that were reviewed in later papers included here [28–32], one mainly focused on emerging treatment research or perspectives [33], two concerned oxytocin but with no specific results in AN [34,35].

The 19 selected papers (15 systematic reviews and four meta-analyses) are presented in Table 3.

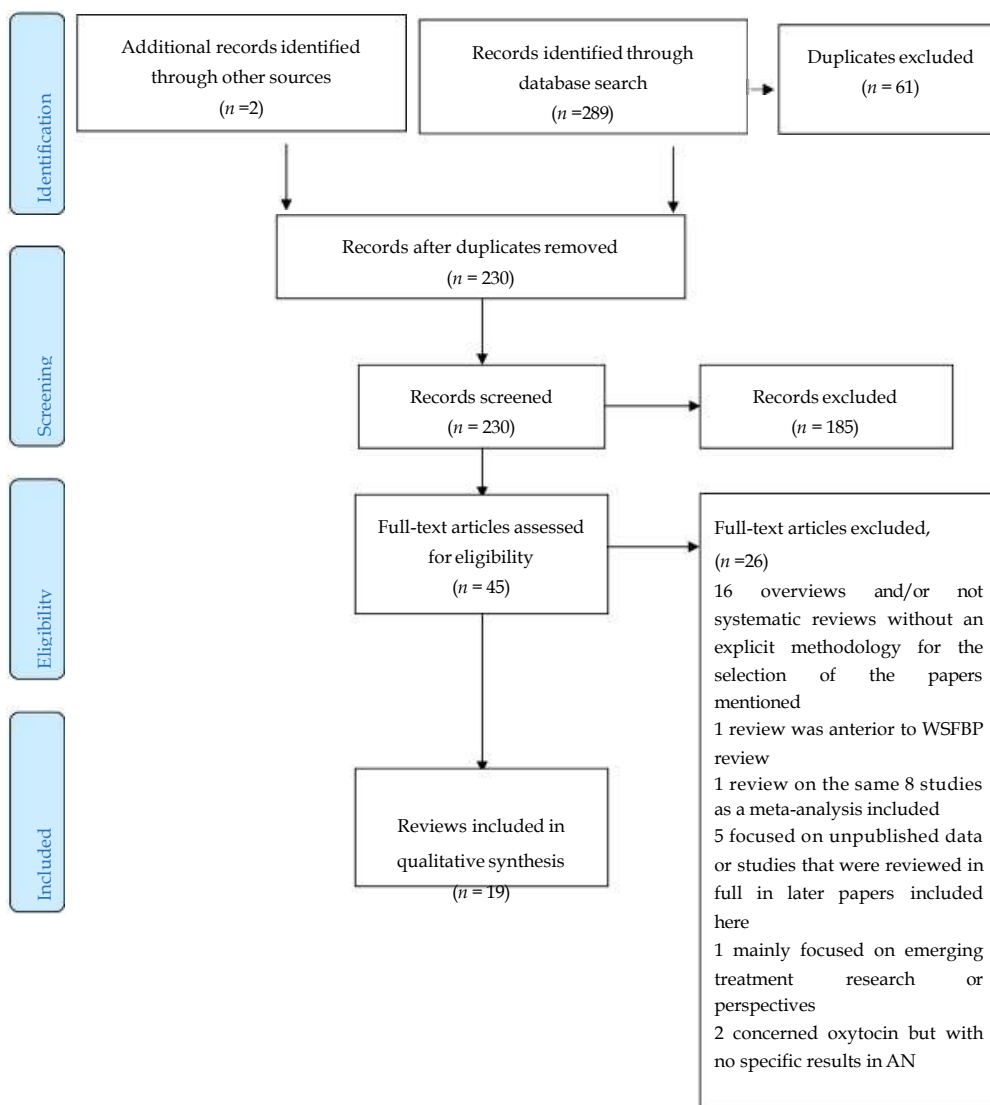


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram [36].

Table 3. Meta-analyses and systematic reviews selected.

Author	Year	Method	Database	Type of Study	Participant Age	Review Period from	Review Period to	Medication
Aigner, M. et al. [6]	2011	Systematic review	MEDLINE	45 studies = 19 open or case studies 26 RCTs	All	1977	2011	Antidepressants; Antipsychotics (typical and atypical); Prokinetic agents; Cannabinoids; Anticholinergics; Naltrexone; Clonidine; Tube feeding; Lithium; Growth Hormone; Zinc
Flament, M. et al. [37]	2012	Systematic review	MEDLINE; PsycINFO	11 RCTs; if none were available (e.g. for paediatric EDS) open trials or case reports suggesting benefits; systemic reviews; meta-analyses; and guidelines	All	1960	May 2010	Antidepressants; Antipsychotics (typical and atypical); Mood stabilizers and anticonvulsivants; Prokinetic agents; Opiate agonists; Appetite enhancers
Kishi, T. et al. [72]	2012	Meta-analysis	PubMed; PsycINFO; Cochrane	SLCR 8 n) scjioqoysdijne jacidjy no s.LCR 8 any form, used for at least 4 weeks) compared to any control intervention on BMI, eating disorder, and psychiatric symptoms in adolescents and adults with AN Eligible studies assessed BMI before, during, and/or after treatment. We excluded studies that enrolled patients who had a primary psychotic disorder.	All	No limitation	March 2012	Antipsychotics (typical and atypical)
Lebow et al. [38]	2013	Meta-analysis	Cochrane; MEDLINE; Embase; Scopus; Web of Science; PsycINFO	10 studies = 8 RCTs, 2 prospective cohort studies	All	1998	November 2011	Atypical antipsychotics
Lebow, J. et al. [63]	2013	Systematic review	Not reported MEDLINE; PsycINFO;	32 RCTs	All	1960	October 2011	Estrogen therapies Antidepressants; Antipsychotics; Cyproheptadine; Recombinant human growth hormone (rhGH); Risedronate; Testosterone; Nasogastric tube
Watson, T. et al. [69]	2013	Systematic review	The Cumulative Index to Nursing and Applied Health; Educational Resources Information Center; National Agricultural Online; Embase Scopus Access; Cochrane Collaboration Libraries	18 studies = (a) RCTs and (b) comparing pharmacotherapy with a placebo controlled condition and reported on (c) patients with Anorexia Nervosa and an age minimum of 12 years. Outcome was measured in (d) terms of weight gain	All	No limitation	October 2012	Antidepressants; Antipsychotics; Hormonal therapy
De Vos et al. [14]	2014	Meta-analysis	PubMed; PsycINFO; Embase; Cochrane Library	scjipnps jnoitvavarsqo L	All	No limitation	May 2012	Nutrition therapy
Rocks, T. et al. [24]	2014	Systematic review	PubMed; Scopus; Web of Science ClinicalTrials.gov; Clinicaltrialsregister.eu;	scjioqoysdijne jnoitvavarsqo s.LCR L efficacy, acceptability, and tolerability in comparison to placebo/no treatment, even unpublished studies	All	No limitation	August 2014	Atypical antipsychotics
Dold et al. [43]	2015	Meta-analysis	Cochrane Central Register of Controlled Trials (CENTRAL); Embase; PubMed/MEDLINE; PsycINFO		All	No limitation	August 2014	Atypical antipsychotics

Table 3. Cont.

Author	Year	Method	Database	Type of Study	Participant Age	Review Period from	Review Period to	Medication
El Ghoch, M. et al. [44]	2016	Systematic review	PubMed	19 studies = 11 prospective non-controlled, 4 prospective controlled, 4 palliatio-nou aipedsorria 4 66 studies = 25 double-blind, placebo-controlled studies; 7 double-blind, placebo-controlled crossover studies; 5 single-blind, placebo-controlled studies; 23 open-label studies; and 6 retrospective systematic chart reviews	11–19 years	No limitation	No limitation	Weight gain and restoration Antidepressants; Antipsychotics (typical and atypical); Mood Stabilizers; Zinc; Opiates and Cannabinoids; Benzodiazepines and Alpha 2 Adrenergics; D-Cycloerine; Amantadine; DHEA; Ghrelin; Growth Hormone; Testosterone; Estrogen
Frank, G.K. et al. [57]	2016	Systematic review	National Center for Biotechnology Information database	27 studies = 1 RCT, 6 prospective, 14 retrospective, 6 observational	All	No limitation	15 March 2015	Refeeding approaches
Garber, A.K. et al. [46]	2016	Systematic review	PubMed; Scopus; PsycINFO; Clinical trials database	18 studies = 2 RCTs, 6 retrospective, 5 cohort, 1 observational, 4 case reports	13–38 years	No limitation	January 1966	Tube feeding
Kells, M. et al. [47]	2016	Systematic review (integrative)	PubMed; Embase; Cochrane CINAHl	41 studies = 17 RCTs, 9 open trials, 12 case series and case reports, 2 retrospective observations, 1 single-blind RCT	11–57 years	No limitation	May 2016	Antidepressants; Antipsychotics (typical and atypical); Lithium; Clonidine; Cyproheptadine
Minati, M. et al. [87]	2016	Systematic review	MEDLINE; PsycINFO	20 studies = 10 RCTs, 8 prospective observational studies, 1 retrospective cohort study, 1 prospective study	Adults	January 1966	January 2014	Weight gain and restoration, Estrogen replacement therapy, recombinant h-GH, recombinant h-IgFL, DHEA, Biphosphonates, Teriparatide
Misra, M. et al. [67]	2016	Systematic review	PubMed	19 studies = 10 double-blind RCTs, 2 prospective observational studies, 1 retrospective cohort study, 1 case-control study and 5 non-randomised control trials	11–45 years	1995	2015	EE/levonorgestrel or EE/progestin or EE/Norgestimate), various oestrogen replacement treatments (transdermal 17βE/progesterone or oral EE/progesterone), Teriparatide (TPP), Alendronate, rhlgFl, Menatrenone (MEI) (vitamin K2), risedronate, transdermal testosterone
Robinson, L. et al. [50]	2017	Systematic review	MEDLINE; PsycINFO; Embase; Cochrane Database	19 studies = 10 double-blind RCTs, 2 prospective observational studies, 1 retrospective cohort study, 1 case-control study and 5 non-randomised control trials	All	No limitation	4102 4p4p4p 3	EE/levonorgestrel or EE/progestin or EE/Norgestimate), various oestrogen replacement treatments (transdermal 17βE/progesterone or oral EE/progesterone), Teriparatide (TPP), Alendronate, rhlgFl, Menatrenone (MEI) (vitamin K2), risedronate, transdermal testosterone
Brockmeyer, T. et al. [51]	2018	Systematic review	PubMed; Scopus; Web of Science	ano gupipjnu) uoitepjpem uo sLJR 9 unpublished study)	All	October 2011 (post Watson 2012)	31 December 2016	Antipsychotics; Dronabinol; Tube feeding
Hale, M.D. et al. [25]	2018	Systematic review	PubMed; PsycINFO; CINAHl; Web of Science; Cochrane Library; Dissertations and Theses	19 open, prospective RCTs, non-randomized controlled trials, prospective cohort studies, retrospective chart reviews	All	No limitation	September 2017	Tube feeding
Rizzo, S.M. et al. [35]	2018	Systematic review	(ProQuest); Google Scholar PubMed; Scopus; Web of Science; PsycINFO	10 studies = 1 RCT, 1 prospective cohort study, 8 retrospective cohort studies	10–57 years	No limitation	May 2018	Enteral Nutrition via Nasogastric Tube

ED: Eating Disorder; BMI: Body Mass Index; EE: Ethinyl Estradiol; GH: Growth Hormone; OC: Oral Contraceptive; DHEA: Dehydroepiandrosterone; RCT(s): randomized controlled trial(s).

Secondly, the overview was completed by original research (RCTs, open studies as mentioned previously) published after the last review or meta-analysis reviewed. In addition, for nutritional and somatic aspects, as there was no meta-analysis nor systematic review on some of the subjects (vitamin D and calcium, micronutrients supplementation and functional digestive disorders), we reviewed published papers (RCTs, and if not open studies as mentioned previously), and retrospective or case studies if no other information existed on the topic of AN. For functional digestive disorders, as there were no papers about their treatment in the AN literature, reviews including this topic (in general and not in AN) were selected.

2.2. Study selection and Quality Assessment

From the French Anorexia and Bulimia Federation (<http://www.anorexiéboulimie-afdas.fr/>), we recruited a group of eating disorder specialists participating on a voluntary basis, including nutritionists, an endocrinologist, an adolescent paediatrician, psychiatrists, and child and adolescent psychiatrists (see authors of the paper).

Eligible papers were screened in the literature search by their title and abstract by two reviewers working together (C.B. and N.G.). The papers were selected by agreement on the basis of the inclusion exclusion criteria (Table 2). Then, the screened papers (meta-analyses or systematic reviews) were read in full and again selected or not, according to inclusion and exclusion criteria. If there was any uncertainty regarding the eligibility of a paper, it was referred to the rest of team for further discussion.

Disagreements between reviewers were resolved by consensus; they mainly concerned the suitability of studies for the purpose of the review.

3. Results

3.1. Papers Selected

The 19 selected systematic reviews are presented in Table 3.

We gave priority here to meta-analyses and systematic reviews rather than to study reports, according to the following rules. For each topic, meta-analysis results are presented first when available. Then, if the meta-analyses only focused on a particular period or a specific question, or if there was no meta-analysis on the topic, the results of the more recent systematic reviews on the topic based on RCTs were described, and completed by previous ones if they provided more information. If reviews on the topic were not available, existing trials on the topic are reported, RCTs are reported in priority if available, if not open trials are reported. Study reports are only cited if they were not referenced in the cited meta-analyses or reviews and were published after the reviews (we did not take into account papers excluded from the reviews for methodological reasons).

We do not report on case reports, or retrospective chart studies, as they are based on the local practice of the teams involved, and are more a reflection of their practice than an evaluation of treatments. In case of numerous reviews or meta-analyses on a topic, results are completed by earlier reviews if they provide complementary information. When samples only involved adolescents, this is mentioned, and any specifics concerning the adolescents are also mentioned.

3.2. Results: Psychotropic Medications

3.2.1. Methodological Issues

The reviews and meta-analyses selected in this overview reviewed from six [51] to 66 studies [45] (see Table 3). This wide range results from numerous factors (aim of the review; types of study considered: ranging from only RCTs to all types of study; period; methodology for selection of studies: ranging from all published studies to a selection based on quality guidelines; type and number of databases used). For example, Brockmeyer et al. used the Cochrane Handbook and the National Institute of Health Criteria for a quality assessment of controlled intervention studies [51]

between October 2011 and the end of 2016 and selected only three good quality RCTs on psychotropic medication. Conversely, Franck et al. [45] were exhaustive and included all studies (except case reports) published in the past 50 years. Miniati et al. [48] underlined the impossibility of applying quality criteria to select studies in their review. In addition, samples were very different in terms of age (see Table 3), some focused on adolescents, others on adults, and some on both.

Psychotropic medications have been used since the 1960s to treat AN. For the studies included in the reviews, Miniati et al [48] underlined the paucity of reports, including the small number of RCTs, the small numbers of subjects included in the studies (one to maximum 93 in this review), the heterogeneity of sample composition, treatments, and treatment settings, and the small number of males to enable comparisons based on gender, which are all aspects that impact the conclusions.

The variable settings (inpatient/outpatient) had an impact on patient characteristics; for example in the studies, these authors observed that the age of inpatients was significantly younger than that of outpatients [48]. In addition, in cases of positive results in favour of a medication, the results had never been replicated. The conclusions of these studies were based on small samples and the fact that they derived no significant results could be partly explained by a lack of power; the results were often extrapolated across patient groups of different ages, illness durations, and severity. Another important limitation of these studies is their duration [48]. Most of the studies were based on short term follow-up in an illness requiring long-term management [48]. The majority of the studies were conducted on inpatient samples, whereas the majority of patients are treated on an ambulatory basis [48]. Not all symptom dimensions of AN, nor all the comorbidities, nor the impact of the medication on these elements were systematically reported.

A small number of studies specially focused on children and adolescents. The majority of the studies were conducted in the acute phase of AN and a minority in the maintenance phase [40]. Below we provide information in terms of dose, duration of treatment, and sample size, for comparative studies only.

3.2.2. Antidepressants (AD)

The rationale for treating AN with antidepressants was initially that AN and depression had clinical and biological similarities, including comorbidity and symptom overlap with anxiety disorders, obsessive compulsive disorders and depression, and a hypothetical dysfunction in the serotonergic and noradrenergic systems in the pathophysiology of AN. The earliest studies mostly concerned tricyclics and monoamine oxydase inhibitors and the more recent mostly concerned selective serotonin reuptake inhibitors (SSRI) [6,37,45,48]. We found one small meta-analysis [41] pooling two studies on tricyclics [54,55], two on selective serotonin reuptake inhibitors [56,57], and five reviews concerning each different class of antidepressant separately [6,37,40,45,48]. No other recent study was found.

Meta-analyses

The meta-analyses (see Table 3 for details) concerned all antidepressant RCTs versus placebo evaluating the impact on either weight restoration or maintenance, with various doses, durations and evaluation criteria. It pooled four RCTs. One was on clomipramine (50 mg, duration not mentioned, there were eight placebo subjects and there were eight AD subjects, evaluation criterion: weight gain in kg) [54], one was on amitriptyline (160 mg max, for 32–45 days, there were 25 placebo subjects, and 24 AD subjects, evaluation criterion: weight gain per day) [55]. Two were on fluoxetine [56,57] (respectively 60 mg and 20 to 60mg, for 7 weeks and 1 year, 16 placebo and 44 subjects, 15 AD and 49 subjects, evaluation criteria, respectively: ideal body weight and body mass index) involving 96 patients in the antidepressant groups and 94 patients in the placebo groups. No impact of antidepressants on weight gain or maintenance in AN was found [41]; because of the small sample sizes no meta regression or subgroup analyses were conducted.

Tricyclics

On the basis of an analysis of three RCTs versus placebo [45,48], there is no clear evidence for the general use of tricyclics among patients with AN in terms of weight gain and depressive symptoms, according to two studies on amitriptyline (160 mg max and 2.8 ± 0.3 mg/kg, respectively for 32–45 days and five weeks, placebo 25 subjects and 11, AD 24 and 11 subjects, evaluation criteria: weight gain per day and weight plus psychological outcome) [58] and one with clomipramine (50 mg, 76 days clomipramine and 72 days placebo, placebo eight and AD eight subjects, evaluation criterion: weight gain in kg) [54,59]. These drugs only showed some impact on hunger, appetite, and energy intake at the beginning of treatment, but with no effect on weight, as mentioned previously. Although clomipramine tended in one study [54] to be associated with lower weight gain compared to the placebo, this was hypothesised to be linked to more physical activity. An open trial comparing paroxetine to clomipramine (respectively 18.4 ± 4.7 mg and 75.3 ± 7.6 mg, duration 39 ± 26 and 58 ± 30 , 39 and AD 57 subjects, evaluation criteria: BMI, duration to weight gain) found no difference in terms of weight gain in an adolescent sample, but duration to obtain weight gain was significantly shorter for paroxetine (72 versus 97 days) [45,60]. In addition, because of the lethal risk with overdose in suicide attempts and the potential for fatal arrhythmia at low body weight, particularly among young subjects, this type of medication is no longer studied and is not recommended today for AN [6,37,40,45,48].

Selective Serotonin Reuptake Inhibitors (SSRIs)

There is today no clear evidence supporting the use of SSRIs in AN [48].

The three RCTs [56,57,61] on fluoxetine versus placebo provided controversial results (respectively 60 mg for the first and for the others 20 to 60 mg, for seven weeks, one year, and 52 weeks, placebo 16, 44, and 16 subjects AD 15, 49, and 19 subjects). Most RCTs with placebo (2/3) reported negative results concerning the effect on eating psychopathology and weight gain [56] and on weight maintenance on a large sample at 12 months [45,48,57]. The only one that had positive results for the maintenance of weight at 12 months and for anxiety [61] had only 13 completers for the treatment and no associated psychological treatment [48]. Some authors hypothesised that fluoxetine inefficacy could be linked to malnutrition, and in particular, to a lack of dietary tryptophan. Tryptophan supplementation in addition to fluoxetine was evaluated in a double-blind controlled trial versus placebo (fluoxetine 20 to 60 mg, for six months, AD and placebo 11 subjects, AD with nutritional supplementation 15 subjects). Barbarich, et al. [62], did not show benefits from this supplementation on weight gain, anxiety or obsessive compulsive symptoms [45]. Three RCTs compared fluoxetine to nortriptyline, amineptine [63,64] (respectively for fluoxetine 60 mg, versus nortriptyline 75 mg, amineptine 300 mg for 16 weeks, 22 subjects and 13 subjects) or clomipramine / amisulpride [65] (respectively for fluoxetine 28 mg, clomipramine 58 mg/ amisulpride 50 mg for 12 weeks, 35 subjects), and failed to demonstrate any difference [40].

The effect of citalopram was only investigated in three open trials [66–68]. The authors of the third study with a control group (citalopram 20 mg, for 12 weeks, 19 subjects compared to 20 patients on a waiting list) found no improvement in terms of weight, but an improvement in depression, obsessive-compulsive symptoms, impulsiveness and trait-anger [48], and body dissatisfaction [45].

A small open-label study that compared sertraline with the placebo [69] reported that sertraline improved depressive symptoms, perceptions of ineffectiveness, a lack of interoceptive awareness, and perfectionism, but not weight gain [45]

Other Antidepressants

Monoamine oxidase inhibitors were evaluated in an open study among six patients for six weeks [70]. Mood and anxiety improved [45] but these drugs are no longer used, as a result of both their inefficacy on weight and their unfavourable side effect profile [48]. Venlaxine has only

been studied in an open trial [71], in comparison with fluoxetine and in association with cognitive behavioural therapy, with no differences in weight or behaviour outcomes [45]. Mirtazapine and duloxetine used in AN have only been described in case reports on adults [48]. Concerning adolescents, mirtazapine was not found to be superior to other medications nor to no medication in AN [45].

In conclusion, antidepressants have no impact on weight gain [45,48], and their impact on eating symptoms or psychopathology is not clear. Tricyclics and monoamine oxidase inhibitors have adverse side effect profiles and should no longer be used in AN [45,48].

Antipsychotics

The rationale for treating AN with antipsychotics was initially linked to the hypothesis that obsessions regarding weight and body shape in AN (abnormal beliefs that are ego-syntonic and characterised by an acute lack of insight that persists even when the affected person's health status is endangered) could be viewed as delusional ideas and consequently could result from dopamine receptor hypersensitivity in AN [45]. Other arguments for their use in AN were based on the effect of these drugs on reward system regulation, their potential efficacy in controlling problematic frequency of physical activity (usually called hyperactivity in AN) and the weight gain side effects observed in other disorders [48]. Another recent argument is that second generation drugs also act on the salience network, known to be impaired in eating disorders, and that they could thus act by enhancing the reactivity of the anterior cingulate cortex and the salience network in the response to the reward value of food in AN. These drugs are mainly dopamine D2 and serotonin 5HT2A antagonists [71]. Finally, more recently, Frieling et al. [72] cited by Miniati et al. [48], have postulated the existence of an altered expression of the dopaminergic genes among patients exhibiting psychomotor hyperactivity. These drugs are dopamine D2 receptor antagonists with severe adverse effects. For second-generation drugs, the arguments also include positive effects on depression and anxiety symptoms arising from eating disorders [48]. First-generation antipsychotics (typical antipsychotics) and second-generation (atypical) antipsychotics have all been studied.

Four meta-analyses [27,38,41,43] and six reviews concerned each class of antipsychotic separately [6,37,40,45,48,51]. The reviews are considered for first-generation drugs, as they are mainly not included in meta-analyses, and also for second-generation drugs after 2012 (the most recent data in the meta-analyses). Since the end of the last review [48] five study reports have been published about antipsychotics in AN, two retrospective chart reviews on adults and adolescents with AN respectively [45] not reviewed here, one open-label study among adolescents [73] and one among adults [74] not reviewed here, and two RCTs [75,76]. Details concerning antipsychotic studies are presented in Table 4.

Table 4. Description of neuroleptics and antipsychotics studies [45,48].

Author	Study	Treatment Group	Daily Medication Dose	Length of Treatment	N	Mean Age ± SD (Years)	Results
Vandereycken and Pierloot, [71] 1982	Double-blind placebo controlled crossover	pimozide placebo	500 or 1000 mg	8 weeks	18	Non reported	Non-significant on weight gain
Vandereycken, [78] 1984	Double-blind placebo controlled crossover	sulpiride /placebo sequence	300 or 400 mg	2–3 weeks	99	23.2 ± 6.5 23.7 ± 9.6	Non-significant on weight gain
Ruggiero et al., [65] 2001	Open-label	clomipramine fluoxetine amisulpride	Mean = 57.7 ± 25.8 mg Mean = 26.0 ± 10.3 mg Mean = 50.0 ± 0.0 mg	8 weeks	10 13 12	23.7 ± 4.6 4.5 ± 5.1 24.3 ± 5.8	No significant difference between groups in term of weight gain significant increase for fluoxetine and amisulpride groups
Cassano et al., [79] 2003	Open label	haloperidol	Months 1–3 Mean = 1.2 ± 0.4 mg; Months 4–6 Mean = 1.1 ± 0.2 mg	9 weeks	13	22.8 ± 4.2	BMI increased significantly in chronic and treatment-resistant patients
Mondravy et al., [80] 2005	Double-blind placebo controlled	olanzapine chlorpromazine	10 mg 50 mg	Mean = 46 ± 31 days Mean = 53 ± 26 days	87 10	25.3 ± 7.42 5.3 ± 7.3	No significant difference in weight gain
Brambilla et al., [81] 2007a	Double-blind placebo controlled	olanzapine and cognitive behaviour therapy and nutritional rehabilitation placebo and cognitive behavioural therapy and nutritional rehabilitation	2.5 mg for 1 month; 5 mg for 2 months	8 weeks	10	23 ± 4.8	No difference for weight gain
Brambilla et al., [82] 2007b	Double-blind placebo controlled	olanzapine and cognitive behavioural therapy placebo and cognitive behavioural therapy	2.5 mg for 1 month; 5 mg for 2 months	8 weeks	15 15	23.7 ± 4.8 26.3 ± 8.5	No difference for weight gain between groups greater improvement on the Eating Disorder Inventory Ineffectiveness and maturity fear scores in the olanzapine group
Bissada et al., [83] 2008	Double-blind placebo controlled	olanzapine placebo	Start = 2.5 mg; Max = 10 mg – flexible dose regimen	10 weeks	16 18	23.6 ± 6.5 29.7 ± 11.6	Olanzapine: greater weight increase and faster achievement of weight goals
Atia et al., [84] 2011	Double-blind placebo controlled	olanzapine placebo	Start = 2.5 mg; Last 4 weeks = 10 mg	8 weeks	11 12	27.7 ± 9.1	Olanzapine was associated with a small but significant increase in BMI compared to placebo
Kafantaris et al., [85] 2011	Double-blind placebo controlled	olanzapine and psychotherapy placebo and psychotherapy	Start = 2.5 mg; week 4 target = 10 mg	10 weeks	10	16.4 ± 2.2 18.1 ± 2.0	No significant difference in weight gain between groups
Hagman et al., [86] 2011	Double-blind placebo controlled	risperidone placebo	Mean = 2.5 ± 1.2 mg Mean = 3.0 ± 1.0 mg	17 weeks	182 7	16.2 ± 2.5 15.8 ± 2.3	No significant difference in weight gain between groups; the risperidone group showed greater reduction in drive for thinness over the first half of the study, but this was not sustained
Powers et al., [87] 2012	Double-blind placebo controlled	quetiapine placebo	Mean = 177.7 ± 90.8 mg	8 weeks	46	34 ± 14.5	No difference between quetiapine and placebo on weight, eating disorders, anxiety and depressive symptoms

BMI: Body Mass Index.

Meta-Analyses

The meta-analyses compared antipsychotics, mainly second-generation, to placebo in six to eight studies, but never exactly the same drugs, always with a majority of studies on olanzapine. 2/4 pooled first and second-generation antipsychotics [27,41], the two others only included second-generation drugs [38,43]. They concerned respectively:

- Eight RCTs (four on olanzapine [81,82], one on quetiapine [88], one on risperidone [86], one on pimozide [77] and one on sulpiride [78] versus placebo) with 102 subjects in the antipsychotic group and 114 in the comparator group (six placebo groups and one treatment-as-usual), one study [78] included one sample of adolescents, the last one [86] examined the effects on BMI, weight, glucose levels, depressive and anxiety symptoms, dropout rates from any cause, adverse effects, akathisia and drowsiness/sedation [27].

- Seven RCTs including five against placebo, four on olanzapine [81–84], one on risperidone [86], and two against chlorpromazine [80] or clomipramine or fluoxetine [65] with 72 subjects in the second-generation antipsychotic group and 75 in the comparator group, exploring weight gain and drive for thinness, body dissatisfaction, overall eating disorder symptoms and anxiety [38,43].

- Six RCTs (five on olanzapine [81,82,84,85] and one on sulpiride [78]), including one sample of adolescents [85], one with 73 subjects in the antipsychotic group and 72 in the placebo group, exploring weight post-treatment [41].

- Seven RCTs (four on olanzapine [81–84], two on quetiapine [87,88], and one on risperidone [86] with 91 subjects in the second-generation antipsychotic group and 99 in the placebo group, exploring BMI change, overall changes in anorectic symptoms, and number of dropouts [43].

No impact of antipsychotics was found in comparison to placebo on weight gain, whether antipsychotics were pooled or considered individually (evaluated in 4/4 meta-analyses), nor on eating disorder symptoms (evaluated in 3/4 meta-analyses [38]), nor was it found for akathisia [27], dropout [27], or glucose levels [27]. A recent paper by Attia et al. [76] reported an RCT on olanzapine increased to the maximum of 10 mg/day in four weeks compared to placebo. This study was conducted on a large sample of 152 adults AN (83 completers) with a long illness duration (mean age for placebo group 28 ± 10.9 and for olanzapine group 30.0 ± 11.0 years old and illness duration respectively 10.5 ± 9.5 and 12.6 ± 11.7). It showed a modest therapeutic effect of four months of olanzapine, compared with placebo on BMI (with an increase difference of 0.165 BMI points more per month). This study found no difference between groups in terms of clinical global impressions, obsessionality, anxiety and depressive symptoms, nor eating disorders symptoms (except an increase in shape concerns that was observed in the olanzapine group).

Drowsiness/sedation occurred significantly more often with antipsychotics than with placebo/usual care in the pooled analyses, and especially for olanzapine in an individual analysis [27]. Attia et al [76] found no significant differences in the frequency of the abnormal blood test to assess metabolic abnormalities between the olanzapine and placebo groups.

For the effect on anxiety and depressive symptoms, there was no apparent efficacy of antipsychotics according to the largest meta-analysis on the topic (pooling four studies) [27]. A recent small RCT study lasting three months among 30 adult outpatients with AN mentioned a superiority of Olanzapine (2.5 mg the first month and 5 mg the two following months) combined with cognitive behavioural therapy (CBT) versus placebo combined with CBT in improving obsessiveness-compulsivity, depression, anxiety and especially hostility (but not weight gain or specific aspects related to the AN eating pathology) without showing results [75].

Typical Antipsychotics other than those Explored in the Meta-Analyses

Haloperidol and chlorpromazine have generally not been evaluated in RCTs, and evidence levels for their efficacy and safety are poor [48]. Haloperidol as an adjunct to psychotherapy was found to be associated with weight over six months in one open study [45,48,79]. In an RCT, there was no

difference in terms of weight gain between chlorpromazine and olanzapine [80] but olanzapine was superior for the reduction of anorexic ruminations [37].

Other Second-Generation Antipsychotics than those Explored in the Meta-Analyses

Amisulpride was studied in one study [45]. It was found to be superior to fluoxetine and clomipramine in a single blind RCT for weight gain (not for weight phobia, body image disturbance or amenorrhea) [65].

Aripiprazole was considered only in a case series of adults and young people [48].

In conclusion, according to the four meta-analyses considered here, antipsychotics had no impact on weight gain compared to placebo, and their impact on eating symptoms and psychopathology is not clear. Olanzapine had a modest effect on weight gain in one RCT including adults with a long duration of AN [76]. Typical antipsychotics have an adverse side effect profile and should not be used in AN, except perhaps haloperidol in severe AN [45]. Atypical antipsychotics could alleviate some symptoms, such as anorexic ruminations, anxiety or depressive symptoms, but levels of evidence are low, and based only on some small studies [75] and not supported by meta-analyses on the topic [27].

3.2.3. Lithium

The rationale for using lithium among patients with AN is mainly related to the fact that it induces weight gain in other disorders [37,48].

We found four reviews concerning lithium [6,37,48] all mentioning one RCT [89], but we found no other recent study.

This small RCT, involving lithium among adults (dose not mentioned, 16 patients and controls, evaluation criterion: weight gain at weeks three and four) showed a significant difference in terms of weight for the lithium-treated group, but not for other psychological dimensions [89]. However, the use of lithium is not recommended in AN, even for patients with severe and resistant forms. Sodium and fluid depletion are frequent in AN and could reduce lithium clearance, which could lead to lithium poisoning [45,48], as renal complications are frequent in AN [90].

3.2.4. Appetite Enhancers

Antihistamines

Four reviews [6,37,45,48] mentioned antihistamines but we did not find any more recent studies.

Cyproheptadine (CYP), a serotonin and histamine antagonist reputed to produce weight gain among children with asthma, was tested in two RCTs [37,48]. The first RCT in four arms compared Placebo and CYP both with and without cognitive behavioural therapy (12 mg to 32 mg maximum, duration not mentioned, 81 subjects in four groups: CYP and behavioural therapy or placebo, placebo and behavioural therapy, placebo; evaluation criterion: weight gain) [91]. The second compared placebo, CYP and amitriptyline (CYP 32 mg maximum, amitriptyline 160 mg maximum, duration: to 5% of target weight, 72 subjects in three groups, evaluation criterion: duration to 5% target weight) [92]. There was no clinically significant effect on weight gain with CYP in the first RCT. In the second, cyproheptadine marginally decreased the length of time to reach the weight gain objective for restricting AN patients, but it significantly impaired treatment efficacy for the bingeing/purging anorectic patients, compared to amitriptyline and placebo [45,48]. Thus antihistamines remain non-indicated in AN and should be avoided. No further study was found.

Opiates

One review [37] mentioned a study about cannabinoids and we did not find any more recent studies.

The opioid peptide system has been implicated in appetite and feeding regulation, linked to the hedonic value of food in both animals and humans. It has been hypothesised that both anorexia

nervosa and bulimia nervosa could be opioid-mediated addictions [37]. In line with these hypotheses opiates and opiate antagonists have been used in order to stimulate eating in AN or to deactivate the suspected auto-addictive properties of food restriction. No study has been conducted in AN exclusively to test this hypothesis. Only one review by Aigner et al. [6] mentions one RCT that was conducted in a mixed sample of 19 AN bingeing/purging subtype and bulimia nervosa patients using naltrexone, 100 mg for 6 weeks [93]. Bingeing and purging behaviours decreased among both AN and bulimia nervosa patients. Naltrexone has no indication in AN.

Cannabinoids

Given the well-known impact of cannabis on appetite, cannabinoids have also been used and tested in AN. [45,51].

Two reviews mentioned cannabinoids, but we did not find any more recent studies [45,51].

Two RCTs evaluated cannabinoids. An earlier four-week double-blind crossover study [45] compared delta-9-tetrahydrocannabinol (delta-9-THC) to diazepam (delta-9-THC, 7.5 to 30 mg versus diazepam 1 to 15 mg, for four weeks, 11 subjects, evaluation criteria: weight gain, daily calorie intake), and showed no benefit of delta-9-THC [94]. In addition, three patients experienced severe dysphoric reactions under 9-Tetrahydrocannabinol administration. The second four-week crossover RCT (5 mg, 4 weeks, 24 subjects, evaluation criteria: weight gain, daily calorie intake), [95] compared low doses of dronabinol (a synthetic form of delta-9- tetrahydrocannabinol) to a placebo and observed a small significant gain of 0.73 kg for dronabinol. It had no impact on the total duration of physical activity but increased the average intensity of this physical activity [51].

In conclusion, cannabinoids have no proof of their efficacy nor of their safety in AN, they need further evaluation in AN, and should not be used in routine care practice.

Ghrelin

One review [45] mentioned ghrelin agonists, but we did not find any more recent studies.

In a small open trial, infusions of ghrelin over 14 days were delivered to five individuals with AN, and improved gastrointestinal discomfort and improved nutritional intake and weight gain were rapidly observed [96].

In conclusion, however, ghrelin has not proved its efficacy nor its safety in AN, and needs more evaluation in that setting.

3.2.5. Other Medications

Benzodiazepines

Only one review mentioned benzodiazepines [45], and we did not find any more recent studies.

Benzodiazepines are anxiolytic agonists of the gamma-aminobutyric acid (GABA) receptors. Although they are widely used in anorexia nervosa [7] studies that systematically investigated benzodiazepines in AN are scarce, and fairly recent [45]. An RCT on alprazolam in an AN inpatient setting comparing 75 mg of alprazolam prior to a laboratory test meal to placebo, did not find this drug beneficial in the treatment of AN [45]: alprazolam does not improve calorie intake and increases fatigue without reducing anxiety [97].

Clonidine

Clonidine is an alpha two adrenergic agonist used to treat hypertension. It was mentioned in only two reviews [6,48] reporting one placebo-controlled crossover study on four patients on 500–700 micrograms/day [98] and we did not find any more recent studies. No beneficial effect in AN was observed, but it was associated with hemodynamic side effects such as hypotension.

In conclusion, clonidine has not proved its efficacy in AN and should not be used in routine care practice.

N-Methyl-D-Aspartate Agonists and Antagonists

D-cycloserine is an N-methyl-D-aspartate (NMDA) receptor agonist known to facilitate extinction learning, a promising treatment for anxiety disorders. Only one review mentioned glutamatergic drugs [45], and they were reported in two RCTs. We did not find any more recent studies.

In one RCT [99], which used D-cycloserine versus placebo prior to meal exposure therapy, it was found that the D-cycloserin group was linked to a greater weight gain after four exposure sessions and at one-month follow-up [45].

The NMDA receptor antagonist amantadine was also used in a case series of 22 patients [100]. Amantadine administered 45 min before the main meal improved neuro-autonomic symptoms during the meal. Patients were able to eat all types of foods and their BMI increased over three months [45].

In conclusion, these drugs have no proof of their efficacy nor of their safety in AN and they need more evaluation in AN. They should not be used in routine care practice.

Oxytocin

Oxytocin is a neuropeptide hormone synthesised in the hypothalamus. It plays a role in pair bonding and in the regulation of broader social interactions, emotional reactivity and feeding behaviours. Some authors suggest that oxytocin could be a useful adjunct for the treatment for AN [51], but no review has published results. We found one recent RCT. The usefulness of oxytocin as a therapeutic agent in AN was tested in only one RCT in the course of hospital-based nutritional rehabilitation, comparing 16 AN patients under oxytocin 36 UI (intra-nasal) per day for four to six weeks and 17 patients receiving placebo. The weight gain was similar in the two groups, while eating concerns and cognitive rigidity lowered after oxytocin treatment [101].

3.3. Results: Somatic and Nutritional Treatments

Recent progress in understanding and progress in care provision for eating disorders has led to an overall consensus at the beginning of the 21st century on somatic and nutritional treatments in multidisciplinary approaches, and on evidence that weight restoration is a key aspect for the correction of many somatic functional disorders. Nevertheless, somatic medications or nutritional approaches for AN patients are more often used off-label, with no detailed guidelines for severe AN inpatient populations, nor for specific organic complications (osteoporosis, growth or puberty failure) treated by various highly specialized physicians.

Our literature review found various narrative reviews concerning somatic aspects of AN, but only a few recent systematic reviews concerning multi-organic somatic medications. In fact, most systematic reviews are concerned with the effects of weight gain or pharmacological treatments (hormone replacement, biphosphonates, teriparatide, and vitamin K) on bone mineral density and secondary osteoporosis [39,44,49,50] or they concerned nutritional therapeutic modalities and their impact on weight changes [42,46], or the efficacy of nasogastric enteral nutrition and adverse effects [47,52,53]. Most of the studies involved small samples, with heterogeneity within and among studies concerning evaluations, biomarkers and age range, with heterogeneous adolescent and adult populations, and various durations, often with an insufficient follow-up. There are very few studies only on child/adolescent populations, and more than 95% of the data mainly concerned female and Caucasian AN patients.

3.3.1. Nutritional Support and Refeeding

While weight gain and progressive weight restoration is an important first step in treating patients with AN, and is essential for medical stabilization before starting specific psychiatric care, it is clear that there is a lack of empirical evidence concerning initial refeeding strategies, and that heterogeneous medical practices are observed in everyday practice.

Approaches to Refeeding

One systematic review [42], including seven studies assessed and summarized nutritional treatments provided for 403 adolescent AN inpatients. Initial energy intake, regardless of refeeding protocols, ranged from 1000 kcal to >1900 kcal/day with a maximum energy intake during hospitalization ranging from 2000 to 4350 kcal/day. The maximum energy intake achieved was greater in the groups with additional enteral feeding (three comparative studies out of seven). The level of evidence for these results was not sufficient to propose any consensus on the most effective refeeding protocols, but it supported the need for future research on this topic.

One systematic review [46], including 27 studies and 2635 patients examined approaches to refeeding among adolescent and adult AN patients in various treatment settings, and 96% were observational/prospective or retrospective and conducted in hospital. This review focused on refeeding protocol analyses, patient clinical characteristics and somato-psycho outcomes. Thirteen studies described a meal-based approach to refeeding (calorie intake divided into meals and snacks), ten studies approached the topic with various combinations of nasogastric feeding and oral intake, one combined total parenteral nutrition and oral intake, three involved altered nutrient content (differing from current dietary recommendations). The main results of this systematic review concluded that the classic refeeding approach (starting the calorie level between 1000 and 1200 kcal/j) among mildly and moderately malnourished patients is too “conservative”, and could be associated with lower weight gain and longer hospitalization. Higher calorie intake (calorie starting level between 1500 and 2400 kcal/j) with a meal-based approach, or a combination of nasogastric feeding and oral intake could be safe and well tolerated with appropriate monitoring. In the absence of sufficient evidence, a lower calorie approach in refeeding remains the rule for severely malnourished inpatients. Parenteral refeeding was associated with multiple adverse effects and is not recommended. The authors of the review suggested more research to evaluate the impact of different refeeding approaches on the duration of a hospital stay and long-term outcomes.

Enteral Feeding (EF)

Enteral feeding is indicated if under-nutrition is severe (BMI < 13) and/or associated with metabolic disorders, and/or if there is prolonged weight stagnation, despite adequate nutritional and psychiatric management [3]. EF is considered safe and well tolerated, and effectively enhances calorie intake and the rate of weight gain among patients with AN [102]. Enteral nutrition should always be performed using a small nasogastric tube. Although a few studies reported using percutaneous endoscopic gastrostomy [103], this route should not be used in the nutritional management of anorexia nervosa, because it can aggravate the distortion of body shape perception among patients. An isocaloric and isotonic solute should be used continuously (1 mL = 1 kcal) in the first days in case of severe undernutrition, in order to avoid post-stimulatory hypoglycaemia [104]; nocturnal refeeding can also be performed. Caloric progression should be cautious in the first days, beginning with 10–15 kcal/kg/d, and increasing slowly up to 30 to 40 kcal/kg/d at one week, in order to prevent refeeding syndrome [105], but some recent data also reported the potential risk of “underfeeding syndrome”, supporting the interest of more aggressive refeeding therapies [106]. EF should be maintained only as needed, to ensure that patients retain normal eating behaviours. Progressive oral feeding should always be encouraged and accompanied by an experienced dietician [107].

One recent systematic review [53] including 10 studies, confirmed that EF is a safe therapeutic tool that is well tolerated for the management of AN patients, with an average weight gain > 1kg/week and enhanced calorie intake and weight gain in the four studies comparing EF to oral-only refeeding. Long-term effects associated with nasogastric enteral refeeding are only reported in the RCT study [108], with a higher mean body weight at 12 months in the EF group.

One systematic review [47] including 18 studies and 1427 adolescent and adult AN patients (1406 F/21 M), evaluated physiological and psychiatric outcomes and patient adherence to nasogastric feeding (NG). It can be noted that 95% of the studies were conducted in inpatient medical or psychiatric

units and only one study concerned ambulatory patients [109]. Continuous NG was reported for 50% of the patients, and various tube refeeding methods (combined, overnight, bolus, not reported) for the others. Mean duration for NG use was 79.5 days. All studies reported a greater short-term weight gain for patients with NG than for patients fed per os, with 30% of non-adherent patients (interference with the tube or the feeding pump). NG could decrease bingeing/purging behaviours and improve cognitive functions and psychiatric comorbidities such as anxiety and depression symptoms. Results concerning the physiological tolerance of NG (digestive disorders), safety (partial symptoms of refeeding syndrome) and the psychiatric outcomes are confusing and should be taken with caution because of the many methodological limitations.

One systematic review [52], investigating the efficacy of enteral nutrition (EN) in the treatment of eating disorders included 22 studies and 1397 AN patients, 97.4 % of whom were females. One study concerned only hospitalized adolescent boys [110]. The nineteen studies evaluating the use of enteral nutrition in the treatment of anorexia nervosa, reported a significant short-term weight and/or BMI gain, but results were more uncertain in the long term. Five studies evaluated the characteristics and outcomes of the use of enteral nutrition in the treatment of binge-eating/purging behaviours, among which four studies were conducted in home settings [108,109,111,112]. The combined results of these studies confirmed that transient exclusive EN use decreased the frequency and severity of bingeing/purging behaviours. Three studies [113–115] on severe AN patients with BMI < 11.5 reported that EN was initially better accepted than oral intake, and that EN is a safe and well-tolerated therapeutic strategy for high-risk patients. No major side effects in comparative studies were reported concerning transient hypophosphatemia, well controlled by biological monitoring, and transient and moderate digestive disturbances were resolved with treatment. Most studies reported various, transient EN interference strategies, without massive refusal for the reinstatement of tube feeding. Hale et al, discussed the limitations of the study, including various selection biases and ethical limitations for the conduct of blind randomized trials in the EN clinical context.

Oral Nutritional Supplementation

High-calorie liquid supplements can be prescribed to supplement oral food intake or to substitute for calories refused in meals, to increase energy intake and to promote weight gain [106]. Different types of oral supplements varying in flavour, volume, and nutritional composition exist, and need to be adapted to individual therapeutic purposes. Evidence is really scarce in the field of AN.

We found no systematic review on this topic, but benefits and adverse effects for high-energy liquid supplements among feeding methods are reported by Hart et al. [116] with the combined findings and conclusions of five descriptive studies [117–120]. Oral nutritional supplements can meet the high calorie requirements for weight gain in a smaller volume (125–300 mL) than food, and can thus be helpful for patients with digestive discomfort and/or for vulnerable patients in avoiding early satiety. This can lead to a better and faster nutritional recovery, and a reduction of hospital stays by shortening the duration of treatment. The main adverse effect is the risk of addiction to oral supplements creating an obstacle to food reintroduction, by reinforcing avoidance behaviours or by encouraging dependence on artificial food sources. These findings suggest that oral nutritional supplements can be considered as a part of dietary and medical care, and should be administered with precise and specific objectives explained to patients and integrated into a multidisciplinary approach.

Parenteral Feeding

Parenteral feeding is contraindicated in anorexia nervosa because of the major risk of metabolic and infectious complications [45].

Micronutrient Supplementation

No systematic review was found on this question. Several micronutrient deficiencies (including vitamins, minerals and trace elements) are described among patients with eating disorders [121]. These

deficiencies are the consequence of restrictive food and low micronutrient intakes widely described among eating disorder patients [122]. Among malnourished patients, initial asymptomatic electrolyte, vitamin and trace element deficiencies can often worsen with re-feeding because of the increased needs, and lead to the occurrence of refeeding syndrome (RS) [45]. Prophylactic electrolyte and micronutrient supplementation is recommended for eating disorder patients with high risk of RS by the French and American guidelines on eating disorders [2,3], especially in long-lasting renutrition among adult AN patients with severe under-nutrition and a very low weight. This supplementation, in addition to unspecific vitamin and trace element supplementation, includes phosphorous (0.5–0.8 mmol/kg/d), and thiamin (200–300 mg/d) [105,123].

Zinc

Zinc deficiency is frequent in AN patients. Zinc is reported to be an appetite stimulator and to improve depression and anxiety. Zinc increases the expression of NPY and orexin m-RNA in experimental animals and plays a role in limiting the progression of cachexia and sarcopenia [124].

One RCT study [125] evidenced a BMI increase that was twice as rapid and an enhancement of brain neurotransmitters, including gamma-aminobutyric acid (GABA), in the group receiving zinc supplementation. No side effects are reported. Birmingham et al [125], suggest that daily oral supplementation should be considered for malnourished AN patients.

Vitamin B12 and Selenium

Other rare micronutrient deficiencies are reported, such as cases of sensory neuropathy resulting from vitamin B12 deficiency [126] and cases of cardiac involvement resulting from selenium deficiency [127]. There are no recommendations on specific supplementation with vitamin B12 or selenium. However, a plasma concentration assay should be performed, and supplementation should be administered if any specific clinical or biological symptoms are observed in severely malnourished AN patients.

Polyunsaturated Fatty Acids (PUFAs)

Polyunsaturated fatty acids (PUFAs) including essential fatty acids, linoleic (n-6) and alpha-linolenic n-3 (n-3) acids, and long-chain fatty acids (LC n-PUFAs), seem to provide different benefits for various neurological and psychic disorders by acting on the brain and the inflammatory system [128].

A recent comprehensive overview of the literature [129] reported that AN patients have modified PUFAs levels. Shih et al [129], reported on one case [130] and two cases series [131,132] concerning the effectiveness of polyunsaturated fatty acid supplementation and concluded that polyunsaturated fatty acids and particularly n-3 and n-6 PUFAs could be a novel adjunct medication for AN patients to treat food aversion, comorbid anxiety and depression and promote weight restoration.

3.3.2. Functional Digestive Disorders

Functional Digestive Disorders according to the Rome III criteria are common in anorexia nervosa [133–135]. Reported lesions are dysphagia and gastric burns, described respectively in 6% and 22% of patients, with no clear link to structural involvement of the oesophagus [136]. In a prospective cohort study including inpatients with eating disorders, 96% reported postprandial fullness, 90% reported abdominal distension and more than half complained of abdominal pain, gastric distension, early satiety and nausea [137]. Classic therapies are not very effective and there are few studies on the subject. Refeeding inducing a return to normal weight, remains the most effective therapeutic option; however no systematic review exists on this topic specifically in AN. We report here, empirical data concerning therapies provided in digestive disturbances associated with AN.

Drugs Acting on the Gastro-Oesophageal Cardia and Gastric Motility

According to the current guidelines of the American College of Gastroenterology [138], the prokinetic agents of choice are metoclopramide, erythromycin, azithromycin, and domperidone [139].

Metoclopramide is the first-line drug (moderate recommendation, moderate level of evidence [138]). It is a dopamine D-2 receptor antagonist that acts by stimulating the parasympathetic innervation of the stomach to increase the motility and contraction of the smooth muscles of the stomach. It should be started at a low dose, 2.5 mg 30 min before meals. This prescription should be monitored clinically because of the risk of acute dystonia and the cardiac risk with the prolongation of the QT interval.

Erythromycin is an antibiotic that also works at low doses, as a motilin agonist, which is a stimulant of gastric peristalsis. It has a prokinetic effect that improves the symptoms of gastroparesis. However, erythromycin has non-negligible adverse effects, and its effectiveness is limited to a few weeks because there is a saturation effect of the receptors. Long-term use can induce a decrease in the response to the drug (strong recommendation and a moderate level of evidence). Moshiree et al, have also shown that azithromycin has a similar motilin agonist effect to erythromycin and can be prescribed at a 250 mg daily dose [140].

Domperidone is a D-2 dopaminergic receptor agonist similar to metoclopramide with fewer central nervous system side effects (moderate recommendation and a moderate level of evidence) [138]. Due to the serious cardiac side effects, domperidone is subject to recent restrictions on use, particularly among underweight AN patients.

Other Drugs for the Gastro-Intestinal Tract

Trimebutine, a smooth muscle relaxant, can be useful in treating irritable bowel syndrome, particularly during the initial re-feeding period [141].

Proton pump inhibitors are often administered to AN patients in a context of gastroesophageal reflux or during tube re-feeding, and they are the first-line treatment because of their efficacy and supposed safety [142]. In fact, proton pump inhibitors have various potential side effects involving bone and renal and digestive functions, and they can interact with psychotropic medications in AN patients [143].

Laxatives

In the context of constipation in AN, the use of laxatives should be evaluated for the risk-benefit balance, and non-irritant osmotic laxatives should be proposed in priority in association with a gut muscle relaxant such as trimebutine. Indeed, they are not very effective, and there is a significant risk of abuse as a strategy for weight control. Their use should be cautious because they can lead to dehydration or hypokalaemia [144], and a progressive withdrawal is necessary to limit sub-occlusive risk.

Probiotics

The gut microflora contributes to the regulation of feeding behaviours and probably has a significant impact on the regulation of responses to stress [145]. Recent findings support the concept of altered host-microbe symbiosis in patients with AN, which could be one of the key factors in the pathophysiology of AN. Probiotic gut microflora modulation could be an interesting biotherapeutic strategy [146,147], but currently no data exists.

To sum up, digestive symptoms are common in patients with AN, they are a source of physical and psychic complaints, and can be a barrier to re-feeding. Functional digestive disorders should be appropriately managed using specific medications restricted in time to relieve patients and facilitate their adherence to the oral or enteral feeding program. Despite the lack of data on their efficacy in AN, these drugs should be considered as an adjunctive therapy on a case-by-case basis among patients with severe functional digestive symptoms, and their relevance should be regularly reassessed.

3.3.3. Endocrine Medications

Anorexia nervosa is associated with numerous neuroendocrine dysfunctions associated with modified plasma hormone levels and blunted, suppressed or paradoxical responses to dynamic tests, involving the hypothalamic-pituitary-gonadal growth hormone (GH)-insulin-like growth factor-I (IGF-I) and the hypothalamic-pituitary-adrenal axis, thyroid function, several adipokines, such as leptin, gut peptides such as ghrelin and YY peptide, and the posterior pituitary (oxytocin and anti-diuretic hormone). Endocrine disturbances can generate severe and irreversible complications involving osteoporosis, puberty, fertility or growth and can in addition perpetuate AN symptoms and psychiatric comorbidities [148,149].

Among AN patients, the majority of endocrine disturbances are attributable to weight reduction and to the low energy availability as a result of chronic starvation, but also due to neuro-psychic alterations, and consequently, the key treatment consists in weight restoration and in treating psychic disorders. Since hormone changes can also act as maintenance or aggravating factors on AN cognitive and behavioural symptoms, on psychiatric comorbidity (anxiety, depression) and on neuro-psychic function, it seems essential not to neglect endocrine comorbidities and to possess an adequate range of specific medications.

To date, no systematic review concerning endocrine medications exists, but we found a few recent, innovative studies on promising hormone treatments conducted among female AN patients: one study concerned recombinant human growth hormone (rhGH) replacement among adult AN women [150], one study concerned rhGH treatment among AN children [151], one study concerned oestrogen replacement among adolescent AN girls [152], one study concerned GnRH among weight-recovered AN [153] and one study concerned recombinant human leptin among underweight women [154]. We report these five studies on these innovative hormone medications in the following sections, and they are summarized in Table S1. All other studies about endocrine medications and bone health and osteoporosis were reported in previous systematic reviews and are summarized in Table 3.

Growth Hormone (GH)-Insulin-Like Growth Factor-I (IGF-I) Axis Medication

Nutritionally acquired resistance to GH, with high levels of this hormone and a disruption of the circadian dynamics of GH secretion, high levels of the GH secretagogue ghrelin, and low serum IGF-I levels have been reported among young AN patients [20]. The pathophysiological mechanisms underlying pubertal delay or arrest and low height velocity (HV) are complex during the critical window for the pubertal growth spurt. These mechanisms can affect adult height, but they are still incompletely understood. After the patients' nutritional and mental state has improved, catch-up growth is highly variable, from complete catch-up to a complete failure to gain height [155,156]. About one third of girls with severe early-onset AN are at risk for adult height deficit [157]. It remains unclear whether the high rates of associated psychiatric comorbidities, such as depression and anxiety, contribute to hypercortisolemia and persistent severe growth deficiency. It can also be noted that among children and adults, GH and IgF1 have various metabolic effects on body composition and trophic effects on bone formation and osteoblastic activity [150].

In a randomized placebo-controlled study, Fazeli et al [150], showed that supraphysiological rhGH administration for AN adult women for 12 weeks failed to increase IgF1 levels, but significantly decreased the total fat mass and fat mass percentage (rhGH, $2.5 \pm 0.6\%$, vs. placebo, $2.2 \pm 1.1\%$; $p = 0.004$) and leptin levels in the rhGH group. Glucose, insulin, free fatty acid levels, bone markers (N-terminal propeptide of type 1 procollagen, type I collagen C-telopeptide), and weight did not differ between the two groups. These results support the independent metabolic roles of GH and IgF1 and the fact that supraphysiological rhGH is not a useful medication for adult AN women because of the negative effects on nutritional status via increased lipolysis, and on gonadal function via the effects of leptin.

In a proof-of-concept study reported by Léger et al [151], recombinant human growth hormone (rhGH) treatment has recently been shown to greatly increase HV among AN adolescents with

delayed puberty and prolonged severe growth failure ($HV < 2.5$ cm/year for at least 18 months at the age of 13.3 ± 1.1 years) within one year of treatment instatement. Serum IGF-I levels increased to the mid-normal range for all patients; HV increased significantly, from a median of 1.0 (0.7–2.1) to 7.1 (6.0–9.5) cm/year after one year ($p < 0.002$). This increase in HV was also maintained in subsequent years and adult height (0.1 ± 1.0 SD) was close to target height after 3.6 ± 1.4 years of rhGH. The treatment was well tolerated. Despite a substantial increase in body mass index (BMI) before the start of GH treatment, mean BMI SDS did not normalize entirely. These data indicate that the increase in HV observed in these patients was probably related to hGH therapy, with only a small potential contribution of the improvement in nutritional intake and BMI. To determine whether hGH therapy should be considered an appropriate option for AN adolescent patients, a randomized placebo-controlled study evaluating the effect of hGH treatment on growth, metabolic parameters, bone mineral density and overall course of the illness in this rare and severe condition in children is currently being conducted.

Hypothalamic-Pituitary-Gonadal Axis Medication

AN patients present functional hypogonadotropic hypogonadism including low levels of gonadal hormones (estradiol/testosterone), prepubertal patterns of gonadotropin hormones (Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), reduced GnRH pulsatility with menstrual disorders in women, and fertility and sexuality disorders in both sexes [149]), although the literature on endocrinopathies among AN males is sparse [158]. Weight restoration is a crucial issue for gonadal function recovery, but individual BMI targets and time lapses to menstrual resumption are highly variable [159], and the indication for hormone replacement to restore menstrual function, and the efficacy of fertility-stimulating treatment among weight-recovered anorexic female patients, are frequently questioned. The potential impact of oestrogen on cognitive function among AN women following adolescent onset has recently been suggested [160].

One double-blind RCT reported by Misra et al [152] on 72 AN adolescent girls with an 18-month follow-up evaluated the impact of transdermal 17 β estradiol (100 μ g twice/week)/ 2.5 mg medroxyprogesterone acetate J1-J10/month) on anxiety, eating attitudes, and body image. Oestrogen replacement was linked to a decrease in anxiety trait scores evaluated on the Spielberger State-Trait Anxiety Inventory for Children (STAIC-trait scores) without impacting anxiety state scores (STAI-state). There was no effect of oestrogen replacement on eating disorder symptoms evaluated on the Eating Disorder Inventory (EDI II) or the Body Shape Questionnaire (BSQ-34 scores). BMI changes did not differ between groups. Oestrogen replacement leads to a reduction in trait anxiety among adolescent girls with AN that is independent from weight changes. However, oestrogen replacement did not directly impact eating attitudes and behaviours, body shape perception, or state anxiety. These results, to be confirmed, raise interesting questions and call for future research to confirm the impact of various oestrogen replacement therapies on cognitive functions, anxiety and depressive symptoms in AN.

One retrospective observational monocentric study reported by Germain et al [153], compared response to gonadotropin-releasing hormone therapy (GnRH) with 20 μ g/90 min/four weeks induction cycles (repeated if there was no pregnancy) administered by a sub-cutaneous infusion pump to 19 weight-recovered AN patients (Rec-AN) (BMI > 18.5) and to patients with other causes of hypothalamic amenorrhea, including primary hypothalamic amenorrhea patients (PHA) and secondary hypothalamic amenorrhea patients (SHA). The study results reported higher estradiol and LH levels during induction cycles among Rec-AN patients than in the PHA and SHA groups; follicular recruitment and the ovulation rate were higher among Rec AN patients than among PHA patients, but similar to SHA patients; the cumulate pregnancy rate was 74 % for Rec-An (vs 73% for SHA et 14% for PHA). No adverse side effect and no excessive response to stimulation were reported. This study showed that pulsatile GnRH therapy could be a safe and efficient treatment in hypothalamic amenorrhea among weight-recovered AN patients.

Leptin

Previous animal model studies reported that leptin, an anorexigen adipokine regulating LH pulsatility, gonadal function, puberty development and fertility, could participate in starvation-induced amenorrhea among AN patients [161]. Leptin levels are decreased in malnourished AN patients, and recent research discussed the potential interest of recombinant human leptin treatment, which could normalize reproductive hormones and restore gonadal function among female AN patients, and the interest of combining recombinant human leptin with oestrogen therapy [162].

One prospective study, reported by Welt et al [154], concerned the use of recombinant human leptin (r-metHULEptin) for up to three months among eight secondary hypothalamic amenorrheic adult women (18–33 years) versus six amenorrheic control subjects. Amenorrhea among the treated patients was secondary to recently increased physical exercise or weight loss but without AN diagnosis. The study reported increased LH pulsatility after two weeks of treatment, and increased estradiol levels and ovarian activity, over a period of three months among treated subjects. Levels of thyroid hormones (free T3), IgF1 and IGF1-BP3 and osteoformation biomarkers also increased with leptin treatment. The safety and tolerance of leptin administration and the impact on eating behaviours among AN patients are in debate and require further research.

There are serious gaps in knowledge and no approved treatment for gonadal deficits or other endocrine dysfunctions in AN despite the various severe consequences on somatic, nutritional and psychiatric aspects of the low levels of reproductive hormones and other hormonal disturbances such as prolonged hypercortisolism. Recent studies suggest interesting new approach strategies, such as sexual hormone therapy to normalize oestrogen deficit, and restore puberty and fertility processes, with a potentially positive impact on cognitive functions, mood, anxiety, and bone health, and reduced spontaneous fracture risk. To date, there is no data concerning gonadal function treatments for male AN patients.

3.3.4. Bone and Osteoporosis Medication

Anorexia nervosa leads to a loss of bone mass, accompanied by low bone mineral density (BMD), secondary osteoporosis and increased fracture risk, as a result of malnutrition and hormonal imbalance [163]. Almost all adult AN patients (92%) have a BMD 1 SD below controls and 38% of patients have a BMD 2.5 SD below controls. For the same duration of amenorrhea, AN patients who develop AN during adolescence have lower BMD than those who present AN later in adult life. As suggested by Misra et al, long-term use of SSRIs could contribute to low bone mass in AN [164]. Given the impact of AN on bone metabolism, fracture risk should be assessed in AN patients using dual energy X-ray absorptiometry (DXA). The U.K. National Osteoporosis Society (NOS) recommends monitoring BMD by DXA every two years.

We found four systematic reviews concerning the treatment provided for bone health and osteoporosis [39,44,49,50]. One of them concerned the impact of weight gain/restoration on bone [44], one was about impact of oestrogen replacement on bone [39], and the two other studies concerned the impact of various somatic medications on bone health [49,50] We report these four systematic reviews in the following sections on the basis of the therapeutic strategies provided.

Weight Gain/Restoration

Restoring weight and normal function of the gonadal axis (with restoration of menses for women) is one of the goals of the treatment of AN and is essential for bone health.

In a systematic review [44] which included 18 studies with follow-up periods from 12 to 90 months of female adolescent AN patients, eight studies showed no significant change in BMD after weight gain/restoration (follow-up 12 months), one study showed decreased BMD after weight restoration (follow-up 12 months), and nine studies showed BMD improvements with weight gain (mean follow-up 30 months) without total catch-up with controls. Therefore, there is strong evidence for at

least a stabilization of BMD with weight gain and/or weight restoration. Longer follow-up (more than 12 months) provides evidence of an increase in BMD with weight gain. Nonetheless low BMD and fracture risk persist after weight recovery. In an adult study [165] the patients whose menses were restored had an increase in spine BMD independently from weight restoration, and weight gain improved hip BMD, whereas the patients with no weight gain nor restoration of menses had an annual rate of BMD decrease of 2.5%. Weight gain and restoration of the gonadal axis can be difficult to obtain in clinical practice. In addition, BMD is persistently low a long time after recovery for AN patients without complete catch-up with weight and menses restoration [166]. The adjunction of complementary medications to treat low BMD and limit fracture risk among pre-menopausal AN women needs to be considered. Only one study [167] on male adolescents with AN was reported, evidencing a rapid and positive bone density evolution in case of weight restoration.

Oestrogen Replacement Therapy

Oestrogen inhibits bone resorption and hypogonadism resulting from food restriction in AN and contributes to increased bone resorption as a result of hypoestrogenia in women.

One cross-sectional study [168] has shown a higher spine BMD for AN subjects exposed to oral contraceptives (OC) combining oestrogen and progesterone compared to AN patients without OC, but Elkazaz et al. [169] reported that healthy premenopausal women with OC current use have a lower BMD compared to women with past OC use and/or non-use, and that this relationship seems in part mediated by IGF1 suppression by oestrogen and thus should not be recommended as a bone accrual medication for adult AN patients.

One systematic review [39] including 10 studies with eight placebo-controlled RCTs evaluated the influence of oestrogen therapies on bone mineral density (lumbar spine and femoral neck or hip BMD by DXA) among adolescent and premenopausal adult women with amenorrhea [39]. Five RCTs used oral contraceptives and three RCTs used hormone replacement therapy. The results were poor quality and generally disappointing regarding oral contraceptives with various ethinyl estradiol doses administered (20–35 µg/d) and various combined progestins, small samples and short follow-up. Of the five studies using oral contraceptives, only one reported increased BMD in the lumbar spine [170], while in the other studies bone loss was not modified or continued to progress. Lebow et al concluded that oral contraceptives were poorly effective in treating bone loss among adolescent or young adult amenorrheic AN patients [39]. Physiological hormone replacement therapy yielded more interesting results, particularly with one study reported by Misra et al, [171] on physiological transdermal oestrogen (17β estradiol) replacement therapy among AN adolescent girls (with incremental doses of oestrogen mimicking oestrogen pubertal secretion for the youngest patients and 100 µg patches for bone-mature patients) combined with cyclic progesterone. This increased hip and spinal BMD, with an increment comparable to the healthy control group, in a well-designed randomized controlled 18-month trial, but it did not provide complete recovery at the end of the trial, as BMD was still lower in the AN group than in the control group [171]. Therefore, transdermal oestrogen replacement therapy, by bypassing the IgF1 suppressive effect of oral oestrogen, could be recommended for adolescent females suffering from AN.

Hormonal and Other Somatic Medications

One systematic review [49] concerning 20 studies (10/20 were double-blind RCTs) reported a synthetic assessment of the effectiveness of weight restoration and interventional studies exploring various somatic drugs (oestrogen replacement therapy, recombinant h-GH, recombinant h-IgF1, DHEA, bisphosphonates, teriparatide) on bone health among adolescent and adult AN women.

The most recent systematic review [50] included 19 studies (10/19 were double-blind RCTs) and concerned adjuvant medications potentially active on bone, such as various oral contraceptives (OC) containing Ethinyl Estradiol(EE)(EE orEE/levonorgestrel orEE/progestin orEE/norgestimate), various

oestrogen replacements (transdermal 17 β E/progesterone or oral EE/progesterone), teriparatide (TPt), alendronate, rhIgF1, menatetrenone (MED) (vitamin K2), risedronate and transdermal testosterone.

The results from these two systematic reviews concerning various medications and pharmacological interventions are summarized in the sections below.

Bisphosphonates

Biphosphonates inhibit osteoclast activity and bone resorption, they increase BMD and reduce fracture risk in post-menopausal women. Three trials have explored the impact of bisphosphonate treatment on BMD in AN (one RCT with alendronate [172], two with risedronate: one controlled trial [173] and one RCT [174]). After 1 year of alendronate in an adolescent AN group (baseline Zscore

• 1), weight was the main determinant of BMD. After controlling for body weight, alendronate increased femoral neck BMD. This does not provide sufficient proof to support the use of alendronate in adolescent osteoporosis in AN.

Among adult premenopausal AN patients with osteopenia (Tscore of -2.7 ± 2) [173] spine BMD had increased by $4.9 \pm 1\%$ after nine months of treatment with risedronate compared to a decrease of $1 \pm 1.3\%$ in the control group. After one year of risedronate [174] (baseline Zscore -1.5 ± 0.7) spine BMD increased by 3.2%, whereas it was unchanged in the placebo group.

Oral bisphosphonates have been associated with upper gastrointestinal tract ulcerations. Nonetheless, in the three trials in AN no adverse effects on the gastrointestinal tract were reported. Intravenous bisphosphonates could be an option in AN, but they have yet to be tested in this population. The main question concerning the use of bisphosphonates in AN resides in its long half-life and its potential harm to the foetus in case of pregnancy. For the time being, for premenopausal adult AN women, the prescription of bisphosphonates cannot be widely recommended, and individual prescription should be discussed on a case-by-case basis.

Testosterone

In the studies using transdermal testosterone administration in women with AN there was no significant changes in markers of bone formation, and no increase in spinal BMD when transdermal testosterone was administered without risedronate [174,175].

DHEA

The sole significant effect of DHEA was observed when combined with oral contraceptive (20 μ gEE/ 0.1 mg levonorgestrel) with a stabilisation of femoral neck BMD [176].

IgF1

RhIGF-1 replacement increased bone formation markers in both adolescents and adults AN patients [177–179]. Effectiveness of combined oral contraceptives or 17 β estradiol replacement and rhIgF1 are discussed [50].

Teriparatide

Teriparatide is a human recombinant parathyroid hormone, anabolic on bone and it is recommended for the treatment of post-menopausal osteoporosis. A six-month RCT [180] studied the impact of teriparatide among older AN patients (mean age 47, Tscore <-2.5), and evidenced that teriparatide increased spine BMD by 6% (+ 0.2% in the control group). This result supports the use of teriparatide as anabolic agent for older AN patients.

Menatetrenone (MED) (Vitamin K2)

Administration of MED (vitamin K2) in AN among Japanese women over a nine-month period reduced bone loss, but there was no increase in BMD [181].

Evidence-based data from these recent comprehensive studies suggests that the safest and most effective strategy to protect and improve bone density in AN and prevent fractures among adolescent and premenopausal women is restoration of weight with the resumption of menses. The most promising available medications include 17 β estradiol replacement (such as the transdermal estradiol patch) for adolescents and bisphosphonates for adults.

Vitamin D and Calcium Supplementation

Low levels of vitamin D and inadequate calcium intake are associated with increased fracture risk and low BMD. In addition, D3 hypovitaminosis could be responsible for the lack of inflammatory response and depressive symptoms among patients with long-term eating disorders. Calcium intake among adolescent AN patients has been described as comparable to that among controls, partly as a result of supplements [182]. While their intake and the bioavailability of oral ergocalciferol among young AN patients was similar to that of healthy controls, AN patients have lower serum levels of 25 and 1,25OH-Vitamin D [183]. In addition, patients who have lower serum levels of vitamin D (<20 ng/mL) have lower hip BMD [184]. After weight gain, the spine BMD increase was greater in the group of patients with higher serum vitamin D levels (> 30 ng/mL) [185], supporting the use of oral vitamin D supplements to obtain sufficient serum levels during weight gain. No RCT prospective trial has been performed to evaluate the efficacy of calcium and vitamin D supplements alone on BMD among AN patients. Nevertheless, given the impact of calcium and vitamin D on bones, although the efficacy of calcium and vitamin D supplementation has been poorly evaluated in AN, we recommend a total intake of calcium of approximately 1000–1200 mg and vitamin D supplements if serum levels of vitamin D are insufficient or if there is a secondary hyperparathyroidism [186]. Since oral calcium supplements can be associated with an increased risk of incident coronary atherosclerosis, a calcium-rich diet should be privileged if possible among AN patients [187].

4. Discussion

The original aim of this multidisciplinary overview was to summarize all the literature published about the use of medication in the psychiatric, somatic and nutritional aspects in AN.

Evidence based on the efficacy of medication in anorexia nervosa is scarce whether for the psychological, somatic or nutritional sphere. The evidence base is sparse, as the literature reports mainly case reports, cases series, open studies and some RTCs. In addition, for the RCTs, methodologies have numerous failings such as the heterogeneity of study designs, research methods, population samples, and intervention modalities [6,37,44,45,50]. The aims of the published research were initially to find medication that would cure AN by overcoming the key resistant symptom, the need for weight gain. Many drugs have been tested in AN on the rationale of their side effect in terms of weight gain in other disorders (for example lithium, antihistamines, cannabinoids, etc.) or their action on clinical manifestations observed in AN (depression, anxiety, obsessions, hyperactivity). In parallel, some psychotropic drugs have been tested in connection with hypotheses of neurobiological etiopathogenic neuro-transmitter involvement in the development or maintenance of AN (for example noradrenalin and serotonin for antidepressants, dopamine for antipsychotics). Recently, new neuro-hormones involved in the regulation of dimensions altered in AN, such as appetite regulation (ghrelin) or social interactions (oxytocin) have been evaluated. However, oxytocin and ghrelin have not proved their efficacy nor their safety in AN. In relation to its anorexigen effect, oxytocin needs more evaluation in AN setting [188]. These neuro-hormones should not be used in routine care practice.

4.1. Somatic and Nutritional Aspects

Concerning somatic aspects, if weight gain is a crucial step to correct the majority of adaptive and functional changes resulting from undernutrition, somatic drugs have been explored from the late 1990s. The evidence of a higher risk of osteoporosis and spontaneous fracture among AN subjects with amenorrhea [17,19] raised the question of the use of bisphosphonate or oestrogen replacement

to treat low bone density [39,49,50]. Other hormone replacement therapies for the endocrine consequences of AN, such as growth or pubertal delay, appeared in the 2000s in association with endocrine-paediatric management in the context of a multidisciplinary approach [151,157]. Two recent narrative update reviews on endocrine mechanisms and repercussions in AN report on available treatments and innovative therapeutic strategies in endocrinology [189,190]. Physicians' interest in refeeding modalities [191], relating to optimal daily calorie requirements [42], the risk of over-feeding and that of under-feeding, high calorie oral supplementation [116], vitamin supplementation and functional digestive disorder medications [139], is fairly recent and corresponds to the development of specific nutritional and dietary expertise, alongside the publication of international guidelines [2,3]. Finally, in the last 20 years, we have observed a paradigm shift concerning enteral tube feeding, considered initially as unethical and coercive, and now viewed as efficient, safe and well tolerated [53]. Promising somatic medications for new targets have developed recently, with micronutrients such as zinc, polyunsaturated fatty acids (PUFAs) used in refeeding, physiological oestrogen replacement or teriparatide to treat bone health, leptin to restore gonadic function, reproductive hormone for hormonal deficits and neuropsychic functions, and GH for severe growth retardation among prepubertal adolescents.

4.2. Psychotropic Drugs

Since the 1960s nearly all classes of psychotropic drugs have been tried in AN [45]. Psychotropic drugs were initially compared to placebo without psychotherapy, with very poor results, but the most recent studies now use psychotropic drugs as additional treatment to global treatment approaches including psychotherapy (individual and/or family therapy). This type of use stems from an international consensus, as attested by the NICE guidelines (the most recent international guidelines published) stipulating that medication cannot be considered as the sole treatment for Anorexia Nervosa (see Table 1).

Despite the evolution and improvement in study design, evidence-based data is scarce and possibly even less robust than it was in the WFSBP in 2011 [6] since atypical antipsychotics seem not to exhibit the efficacy they initially appeared to have.

The RCTs generally evidence negative results concerning weight, and contradictory results concerning eating disorder symptoms and psychiatric dimensions. This situation can be explained by discrepancies in study methodologies [45,48], including many limitations such as relatively short durations of treatment (weeks, or two to three months mainly) and the small sample sizes (fewer than 100 in RCTs, and generally fewer than 30). That said, one of the most important limitations to efficacy in AN is non-compliance with medication treatments: patients frequently do not take their medication.

This situation of a poor evidence base in the existing literature is discouraging [48]. It has led, in the more recent reviews published, to giving prominence to emergent or promising interventions and recommendations for research [24,40,45,51].

In this situation, if we refer only to the evidence-based elements, psychotropic drugs should not be prescribed in AN. However, the reality in the field is quite the reverse. All psychotropic drugs are widely prescribed to both adults and adolescents with AN, and this seems to be increasing [7]. In addition, more than half of the patients have more than one psychotropic drug prescribed simultaneously. Also, dangerous drugs such as bupropion or tricyclics, are still prescribed despite the conclusions of the literature [7]. The same observation has been made in other studies on adults and adolescents in different countries [7,8,192]. These papers highlight the disparity between research conclusions and clinical practice in the treatment of AN. This underlines the importance of consensual guidelines incorporating evidence-based data. We also need expert consensus and training for practitioners on this question, especially for ED specialists, who mostly base their practice on their experience and who seem more resistant to using guidelines than general practitioners [7]. Our "experience" is the result of a complex combination of elements. It is based on core beliefs derived from different sources, including, of course, evidence-based data. Evidence can be biased in favour

of drug efficacy by the publication of positive results only [7]. In addition, some studies (or their coordinators) are sponsored by the industry and their results can be biased by conflicts of interest. This last point leads the latest NICE guidelines to exclude studies sponsored by the industry from the studies analysed to establish the evidence base retained for the guidelines [4]. In addition, our experience is also impacted by psychiatric theoretical orientations, [7] or good or bad experiences with one or several patients.

4.3. Use of Psychotropic Medication in AN

Once we have discussed these elements, the central question for this review is still unresolved: how should we use medication in AN?

As recommended by most guidelines, we need to evaluate the global situation of the patient, including psychiatric, medical, nutritional and social aspects, to propose the best-suited treatment. Medication should be prescribed on the basis of the clinical evaluation. This evaluation should include the patient's opinion about the treatment [4,24].

Concerning psychotropic medication, comorbidities (including mood disorders, anxiety disorders, obsessive disorders) should be evaluated and treated [18,45] if they are real disorders and not "artefacts" that will improve with re-feeding [193]. These disorders are usually treated by teams on the assumption that treating anxiety and depressive disorders facilitates AN treatment, or at least improves their quality of life [45]. These disorders are usually treated according to the specific recommendations for each, and taking into account the particular risks of side effects resulting from low weight and metabolic disturbances (possible depletion in potassium, phosphorus, magnesium, and zinc), and somatic complications concerning hematologic, renal, hepatic and heart functions that can interact with medication. Antidepressants and atypical antipsychotics are the most frequently evaluated drugs and the most widely used in practice.

Chlorpromazine is no longer used for AN because of its severe adverse effects, including seizures; low doses of haloperidol could be effective as an adjunct treatment for patients with severe, treatment-resistant conditions with marked self-image alteration [48]. Atypical antipsychotics can sometimes be useful to help patients with AN, in case of high levels of anxiety [75] or in adults with a long illness duration [76], but practitioners should be aware that they prolong the QT segment and can be dangerous in case of malnutrition by leading to cardiac death associated with ventricular arrhythmia. Their prescription should be monitored for safety, including regular electrocardiogram and ionogram assessments. In addition, because of the risk of metabolic syndrome, such as hyperglycaemia, dyslipidaemia or HTA, the usual guidelines for the monitoring of antipsychotics should be applied. Benzodiazepines are also widely used and their use is questionable, especially among young people, as they induce dependency and can lead to abuse or misuse [7].

A psychotropic drug can be useful to manage eating disorders or psychiatric symptoms. Himmerich et al. [194] in a recent survey among AN patients and carers and reported that people with anorexia nervosa want medication to help with anxiety and sleep problems [24]. However, the specific treatment of AN also requires re-feeding, and/or cessation of bingeing and purging, specific psychotherapy (individual or family therapy) and work on the social impact of the illness. Medications, and especially antidepressants, are less effective among those that are acutely ill and underweight [18].

Outside situations of emergency (suicidal ideas or risk, very severe anxiety or OCD), following the discussion with the patient, it is possible to wait a few weeks in order to later reassess the need for specific treatments for possible comorbidities [195]. In order to diagnose whether psychiatric symptoms are linked to a comorbid diagnosis or to malnutrition, it is useful to investigate the personal and family history of comorbid disorders and the chronology of appearance of AN and psychiatric symptoms. Diagnosis should be based on symptoms, their evolution, the chronology of onset and individual and familial history of comorbidities [18].

A general discussion with the patient (and the parents for a minor) is necessary to review side effects, risks, benefits, and alternatives. One important point to make is that psychotropic drugs do not

induce weight gain in AN but can alleviate negative psychological symptoms. This will be important for the therapeutic alliance. Practitioners should always have in mind that to be efficient, a medication needs to be taken, and AN patients are often not observant, especially for antipsychotics [37]. In addition, to be efficient, a medication needs to be absorbed. When patients purge after they have taken their pills or have swallowing phobia or food orality disturbances, they cannot be efficient. Both points should be discussed with the patients.

As in other reviews, we will conclude on perspectives for future research on the topic of medication in AN.

4.4. Perspectives

Several perspectives suggest the need for the development of innovative treatments.

Part of the lack of evidence could be attributable to the heterogeneity of significant symptoms and the treatment responses encountered in AN. Very few studies thus far have stratified the subtypes or clinical features of the disorder. Anorexia nervosa is a heterogeneous disorder and a single “optimal” drug for all individuals is highly unlikely. Targeting more homogeneous subgroups could be helpful. Thus, growing evidence derived from various approaches supports a specific staging trajectory for anorexia nervosa, and there is preliminary evidence that interventions should be matched to the stage in the illness (for review see [196]). Interventions tailored according to the stage of the illness or the developmental trajectory could be valuable options. Certain other clinical features could be considered for more homogeneous subgroups of patients, since they could be associated with a specific form of the illness, or lower response to medication, for instance the AN subtype (AN-R, AN-BP, AN/B, AN/P), age (differentiating pre and post-pubertal adolescents and adults), gender, cultural environment, current and maximum pre-treatment BMI, associated personality traits, psychiatric comorbidities [45] or a history of childhood abuse [197,198]. A number of latent class and latent profile analyses have been performed on symptom and personality factors to stratify the endo-phenotypes spanning AN [197,199–201]. These sub-categorizations could be a starting point to homogenize samples.

Also, there is currently emphasis on using precision medicine to identify targets, which should lead to more effective treatments. Symptoms that maintain the disorder may differ across individuals and participate in the lack of evidence. A novel methodological perspective is thus to address the extreme heterogeneity within AN and to develop and adapt treatments to each individual, which could be of considerable interest in the near future [202].

Finally, beyond a categorical approach, treating one or several specific dimensions associated with the illness rather than the illness overall could be useful, since changing targets might change clinical outcomes. Some salient dimensions in AN, such as delay discounting or cognitive impulse control, could potentially be targeted by drugs or a neuromodulation approach [203].

Concerning non-psychotropic drugs used in AN, these are mainly used to treat medical conditions associated with AN. It is critical to underline that weight gain and restoration of normal weight is the first line of approach to the management of these conditions whenever possible. Therefore, refeeding modalities for weight gain or restoration, including the specific indications for enteral nutrition, oral nutritional supplementation, micronutrient supplementation and specific drugs for functional digestive disorders, seem absolutely essential, but to date no guidelines exist on nutritional therapeutic strategies for AN.

Among the drugs available, sex hormone treatments need to be discussed, as they are fairly widespread in use, but their effects are a source of considerable debate. Various arguments should be taken into account in the assessment of the risk-benefit balance of their prescription. As demonstrated by our results, oral contraceptives have failed to show any significant benefit in protecting bones among patients with AN. Although certain issues could explain this lack of effect, such as the heterogeneity of the patients included across studies, and variable treatment and follow-up durations, the suggestion is not to use oral contraception to protect bones in AN. On the other hand, transdermal estradiol

has been found to be a more physiological form of oestrogen replacement and more promising than oral administration in managing osteopenia among adolescents with AN. This explains the position of the recent British national guidelines suggesting hormone replacement therapy with 17- β -estradiol (with cyclic progesterone) rather than oral contraception, and only for young AN women (13–17 years). Furthermore, the decision to prescribe oral contraception is not without drawbacks. For example, the return of menstrual function, which indicates adequate weight restoration, is masked by the cessation of bleeding induced by contraceptives. Also, its use can provide a sense of reassurance that patients are protected against osteopenia, which can reduce efforts for weight rehabilitation. On the other hand, it is important to keep in mind that amenorrhea, occurring in 66 to 84% of women suffering from anorexia nervosa, favours the absence of contraceptive measures, explaining a particularly high rate (up to 50%) of unwanted pregnancies in this population. Finally, somato-psychic tolerance and compliance with hormonal replacement are very limited due to fat phobia, menstruation and bleeding refusal in many adolescent AN patients. Recent studies evaluated the interest of testosterone replacement therapy in AN women based on the fact that hypothalamic amenorrhea is associated with a profound androgen deficit. Transdermal testosterone replacement increases spinal BMD when administered with risedronate and can stimulate bone formation [174]. In addition, this could be an effective medication in women with treatment-resistant depression by improving depression and cognitions [175]. Otherwise, as mentioned previously, SSRIs seems to be inefficient in conditions of undernutrition, and future studies should assess optimal renutrition and adapted hormone replacement to potentiate the effectiveness of psychotropic medications [49]. To date, testosterone replacement therapy is not recommended for female nor for male AN patients. Concerning the use of medications for bone health and BMD improvement, despite the promising results of studies on sexual hormone replacement, bisphosphonates and combined interventions among adolescent and premenopausal women, the safest and most effective strategy to protect and improve bone density and prevent spontaneous fractures risk is, for now, the restoration of weight and menstrual recovery. Further studies are needed to establish standards for the treatment of osteoporosis in AN.

There are no specific treatments taking into account particular aspects of adolescent or adult male AN patients and current proposed treatments are similar to those for AN women [158]. Specific research on the male AN population is insufficient and needs to be developed, particularly with regard to testosterone and other therapies, and the benefits of specific drugs on somatic, cognitive and psychiatric functions that can influence evolution and prognosis in AN boys and men.

4.5. Strengths and Limitations of This Overview

As stated by Pollock et al. (p16) [204] “overviews are a relatively new methodological innovation, and there are currently substantial variations in the methodological approaches used within different overviews”. We defined a methodology for this overview on the basis of elements from the literature, but due to the characteristic of the literature concerning medication for AN we could not totally fulfil all the quality criteria previously defined [205].

Indeed, a good quality overview should include systematic reviews with four characteristics [205]: 1. They should not substantially overlap. 2. They should focus on the precise question asked by the overview. 3. They should be high quality. 4. They should be up-to-date.

There is considerable overlap between reviews and meta-analyses selected in our overview. In order not to bias our conclusions we focused on the more recent reviews or meta-analyses; when meta-analyses and reviews were available on the same studies we focused on the meta-analysis conclusions, and when two reviews were available we focused on the more recent one including the more recent research. We selected only systematic reviews with a well-defined methodology but methodological quality was not homogeneous.

The conclusions we have drawn are limited by the methodology of the systematic reviews included, which use different criteria and objectives, over different periods, possibly leading to

different conclusions and possibly biased by their selection. In order to alleviate this limitation we developed a systematic overview using the PRISMA guidelines, mainly based on meta-analyses and systematic reviews of RCTs and open comparative studies, but not on narratives reviews, retrospective studies or case reports.

Our findings are also limited by the quality of the published literature on the topic of medication for AN, which also impacts the conclusions, since most of the studies published on the subject are open studies, retrospective studies or case series or case reports, and RCTs are rare. The reason for this situation is linked to both AN patient refusal to participate in RCTs and to the clinical context, and also to the relatively low frequency of AN. Otherwise, it is also linked to ethical reasons, particularly on the refeeding topic [52] or growth hormone replacement [151]. In addition, the existing RCTs are poor quality, as they were conducted with various methodological procedures, on heterogeneous, small samples, and over different durations of follow-up. Finally, these studies were mostly conducted over short treatment durations whereas AN is a chronic disorder.

5. Conclusions

Perspectives for future research on medication in AN should include more specific phenotyping for psychological dimensions and comorbidities, also taking into account more somatic and anthropometric data, such as pre-morbid weight, body composition, nutritional and hormonal markers of undernutrition, so as to optimize the assessment of the efficacy of medication.

There is a need to make progress and develop innovative therapeutic strategies, especially for severe, chronic forms of AN with resistant psychiatric comorbidities, and for pre-pubertal AN patients with severe somatic prognosis, by targeting medication more efficiently through improved understanding of their etiopathogenic mechanisms [189,190]. A future perspective is to address the extreme heterogeneity within AN and to develop psychotropic treatments for the various clinical dimensions observed. We should develop new, more sensitive and specific biomarkers, especially for bone microarchitecture, because evaluating BMD is not sufficient to predict fracture risk. In addition, we need better-adapted techniques to measure the benefits of weight gain and nutritional status, including body composition analyses [176].

There are exciting perspectives for the development of transdisciplinary studies, based on well-defined and phenotyped sub-groups, including psychotherapeutic approaches and evaluating the impact of optimized refeeding modalities, hormone replacement, other somatic medications, or psychotropic drugs.

Studies should evaluate synergistic benefits of these combined interventions on a global perspective, including renutrition, cognitive functions, somatic, and psychic outcomes over prolonged follow-up periods.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2077-0383/8/2/278/s1>, Table S1: Selected studies concerning innovative hormonal medications for female patients with AN and/or hypothalamic amenorrhea.

Author Contributions: Conceptualization, C.B., S.G., F.B.-P. and N.G.; methodology, C.B., S.G., and N.G.; validation, C.B., N.G., C.S. and S.G.; investigation, C.B., S.G., F.B.-P., M.-E.C., J.C., V.D., P.D., P.G., M.H.-G., S.I., J.L., B.S. and N.G.; resources, C.B., S.G., F.B.-P., M.-E.C., J.C., V.D., P.D., P.G., M.H.-G., J.L., B.S. and N.G.; writing—original draft preparation, C.B., S.G., M.-E.C., F.B.-P., J.C., V.D., P.D., P.G., M.H.-G., S.I., J.L., B.S., C.S. and N.G.; writing—review and editing, C.B., S.G., N.G.; project administration, C.B., N.G.; funding acquisition, C.B., S.G., F.B.-P., V.D., S.I., J.L., B.S. and N.G.

Funding: This research was funded by French Federation Anorexia Bulimia for translation and publication fees.

Acknowledgments: To Angela Verdier for reviewing the English of this paper, and to Wayne Hodgkinson for his friendly participation.

Conflicts of Interest: The authors have no conflict of interest to report. Except: S Guillaume reported that he received funding as a consultant by Janssen, Otsuka and Lundbeck Companies. J. Léger is currently investigator in a clinical trial using growth hormone (GH) from Novo-Nordisk, has received support for travel to international meetings from several GH manufacturers (Ipsen, Merck, Novo Nordisk, Lilly), fees for lectures from Ipsen Pharma and Merck, and consulting fees from Sanofi Genzyme.

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ARTICLE 3

Une PERSPECTIVE de MODELISATION de la TRANSDISCIPLINARITE dans le CHAMP des TROUBLES des CONDUITES ALIMENTAIRES

Le troisième article est un article théorique d'hypothèse médicale s'attachant à étudier le concept de la "transdisciplinarité" et évaluer sa pertinence dans le champ des TCA. Il a été soumis en octobre 2019 à la revue *The Lancet* (revue indexée dans Medline, Impact Factor 2019 : 59.02).

Si les deux premiers articles illustrent la recherche transdisciplinaire, le troisième article correspond à une recherche théorique sur la transdisciplinarité. Cette dernière est-elle transdisciplinaire ? Si nous considérons que la pensée de l'auteure n'est pas une pensée disciplinaire mais une pensée construite par une expérience et dans un environnement institutionnel transdisciplinaires nous serions légitime à le suggérer. En tout état de cause nous pensons pouvoir affirmer que la conceptualisation de cet article a été rendue possible par une position métadisciplinaire de l'auteure²¹.

L'article présenté est une hypothèse médicale, qui comme tous les (trop rares) articles de cette catégorie répond à deux objectifs principaux : "servir de forum pour le travail théorique en médecine et faciliter la publication d'idées potentiellement radicales. Les hypothèses médicales sont particulièrement importantes dans un domaine comme la médecine intégrative" (Wardle, & Rossi, 2016).

²¹ La métadisciplinarité est décrite dans le tableau 2, chap. I a.ii page 21-24

Cette catégorie d'article nous a donc semblé particulièrement adaptée aux approches intégratives des TCA en médecine de l'adolescent, et à notre sujet de recherche. Nous avons considéré qu'elle nous permettrait de partager nos idées avec l'ensemble des disciplines impliquées auprès des patients souffrant de TCA et plus largement avec tous les scientifiques intéressés par les liens entre médecine et sciences humaines.

Ce travail nous permet de relier de façon tout à fait innovante, le concept de transdisciplinarité au domaine des TCA, ce qui à notre connaissance n'a jamais été proposé. L'auteure a été confrontée à deux niveaux de difficultés : la nécessité de recherches dans des champs épistémologiquement très diversifiés, mais aussi et surtout la nécessité de s'extraire de la réalité concrète transdisciplinaire de son environnement quotidien pour théoriser la transdisciplinarité dans le champ des TCA. Nous définissons le "champ TCA" puis nous décrivons comment il s'est progressivement construit autour du patient souffrant d'un TCA et plus symboliquement autour des "figures anorexiques" au fil des époques (Raimbault, & Éliacheff, 1996). Nous montrons enfin la nécessité du concept de transdisciplinarité pour décrire le "champ TCA".

Cet article qui vient clôturer ce travail de thèse, reliant pratique et théorie, est à la fois un aboutissement mais aussi une étape vers un projet plus ambitieux de modélisation de la transdisciplinarité dans l'espace complexe des TCA, pour lequel notre réflexion actuelle porte sur les choix méthodologiques, en particulier le choix des bases théoriques permettant de construire notre modèle.

Ce travail a fait l'objet d'une communication orale lors du 16^{ème} congrès de l'ECED à Paris, en Septembre 2019 : plenary session : "A transdisciplinary Approach of Eating Disorders. C.Blanchet, N.Godart".

Soumis en Octobre 2019

TITLE

Transdisciplinarity invited to the eating disorders table: a challenging model in perspective

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ABSTRACT

Transdisciplinarity, a concept stemming from the humanities, follows on from the explosion of knowledge and the need for reunification of the perspectives of various disciplines around a given object in science and around the patient in medicine. Understanding and therapeutic approaches to eating disorders (ED) – complex and chronic conditions linked to psychogenetic vulnerability factors - have recently evolved, through the crossing views of medicine, neurosciences and humanities. The patient affected by ED convenes, in different contexts, various protagonists with their own perspectives, generating multiple concepts and interactions mobilized "between, across and beyond" disciplinary boundaries. We suggest that transdisciplinarity should be invited to the ED table as an essential component to model the so-called "ED field". This unifying concept of the hypermodern era, reconciling medical theory and practice, is an innovating model for a humanistic and integrative approach providing various applications in care and research methodology for patients with ED.

Key Words : Transdisciplinarity; eating disorders; anorexia nervosa ; epistemology ; model ; care ; research

ARTICLE

Eating disorders (ED) are complex and chronic illnesses that reached the medical sphere in the 19th century *via* the secularization of anorexic figures.¹ In Western countries, ED are currently defined by the DSM5 categorical classification², completed by multidimensional³ and transdiagnostic nosographic approaches⁴. While major advances have been noted in the field of ED over the past two decades, current care result from a challenging and painful trajectory for patients, families and healthcare professionals. In two centuries, a major paradigmatic shift has been observed in the etiopathogenic understanding of ED, the therapeutic framework and the philosophy of care. Understanding of these conditions and their care evolved from the individual, alienist conception of the illness associated with a monodisciplinary patriarchal dogmatism in the 19th century, to a predominant psychoanalytic model in the middle of the 20th century, and then to psychodynamic approaches and a progressive diversification towards multi- or interdisciplinary individual and family-based treatments. At the beginning of 21st century, bio-psychosocial theory⁵ and interdisciplinary holistic understanding models^{6,7,8} accompanied the current integrative approach, which integrates knowledge and skills from various medical disciplines, from the neurosciences and from the humanities, achieving a wide consensus in the international literature and guidelines for ED^{9,10,11}.

In Europe, after centuries of scientific positivism inherited from Cartesian ideology, the proliferation of knowledge and the “Big Bang” of disciplines met the “structuralism crisis“ (1950-1970) and the aspiration towards a global vision of knowledge encompassing different perspectives of disciplines. The various problems associated with disjunctive approaches in the humanities and the exact sciences led to the need to bring disciplines together, to build bridges between them and to determine a unifying concept. The various levels and modes of “multiple-discipline” exchanges have given rise to numerous terms (multi- inter- transdisciplinarity etc.) and typologies¹². Transdisciplinarity, appearing in this “semantic quagmire“¹³, as a polysemic term, should not be considered solely as the ultimate stage in a hierarchical gradation of knowledge towards complexity. All these concepts could be complementary, in an integrative and unifying view, allowing different levels of

interaction between disciplines belonging to epistemologically more or less distant subsystems^{13,14,15}.

Transdisciplinarity is a concept stemming from the human and social sciences, introduced by Jean Piaget (1896-1980) in France in 1970 on the occasion of the conference of the Organization for Economic Cooperation and Development (OECD)¹⁶. Etymologically, the Latin prefix "trans" means across, beyond, through, changing thoroughly and "disciplina" means education, knowledge or a set of laws, rules, and constraints defining a subject, and also a group. Twenty years later, the International Center for Transdisciplinary Studies (CIRET) was created¹⁷. The Transdisciplinarity Charter, adopted during the first World Congress on Transdisciplinarity in Portugal in 1994, specifies the deontology and the immutability of the transdisciplinary stance. In Europe, the leader of transdisciplinarity, the French quantum physicist Basarab Nicolescu (1942-), has defined transdisciplinarity as an intellectual stance and a complex space of thought which is at once "between, through and beyond any discipline". Transdisciplinary methodology is defined by three axioms (ontological, logical and epistemological) that are related to the levels of reality (defined by Edmund Husserl (1859-1938)), the logic of the included middle (defined by Stéphane Lupasco (1900-1988) and complexity¹⁸. Transdisciplinary "understanding" is distinct from disciplinary "knowledge" in particular by the inclusion of values related to a humanistic approach¹⁸. In medicine, the multi-, inter- or transdisciplinary approaches have been historically developed for chronic, severe and unstable conditions such as intellectual deficits in children, severe epilepsy or end-of-life conditions. More recently, transdisciplinarity has been applied to diabetes, obesity, as well as psychiatric or neurodegenerative pathologies requiring the integration of diverse sources of knowledge and various disciplinary interactions. Surprisingly, while the term "transdisciplinarity" has gradually invaded the language and discourse of professionals involved in the care of patients with ED, the concept of transdisciplinarity is most of time inappropriately used, misunderstood, and insufficiently exploited in the field of ED. In September 2019, at the 16th edition of the European Council on Eating Disorders (ECED) "transdisciplinary approaches" were finally discussed for the first time, in order to improve the care pathways of patients affected by ED¹⁹.

Concerning ED, historically, the space of knowledge and clinical action was built around the anorexic figure derived from a long matrilineal filiation¹. All patient with an ED, on account of its high level of complexity, convenes both psychiatric and somatic disciplines (endocrinology, nutrition, adolescent medicine, pediatrics...), neurosciences and also the different methods of psychology, the others human sciences and the social and educational sciences. Progressively, the involvement of more or less epistemologically distant disciplines and of various protagonists has led to the construction of a complex space which is composed of a set of interdependent subsystems, maintaining direct or indirect reciprocal interactions “between, through and beyond” boundaries, as well as including many levels of reality. This so-called “ED field” is a system composed of various interactive subsystems: the first (“environmental”) concerns interactions of the patient with the systemic sociocultural and familial environment and interactions with the peer group; the second (“care setting”) concerns the implication of somatic, nutritional, psychiatric, neuroscientific and psychosocial disciplines; the third (“collaborative stakeholders”) concerns interactions with user associations, regional and national networks and institutional partners or public authorities. A fourth subsystem (“epistemological”) concerns cross-sectional concepts cutting across the “ED field”, derived from the epistemology of the anorexic figures and collective approaches to ED, as well as from the epistemology of the human sciences.

The basic postulates of transdisciplinarity seem particularly relevant to describe the field of ED, for the following reasons:

- The ED field is complex and is constructed around a complex object which is the historical figure of an adolescent female with anorexia nervosa
- The suffering young person, and the real and symbolic value of his/her rebellion, convenes, gathers and interacts with the protagonists
- The existence of diverse subsystems (environmental, care, collaborative) and of different levels of reality (beliefs, theoretical frameworks and practices) for every person implicated in each subsystem¹⁸

- Helping people with ED requires an understanding of these various complementary and non-exclusive theoretical and clinical approaches by using the logic of the included middle to counterbalance the logic of the excluded middle (i. e. binary logic)¹⁸
- The reciprocal interactions "between, beyond and across" the permeable boundaries of these systems enable a sharing of knowledge, skills or tools across disciplines, professionals and other protagonists
- This collective knowledge (*gnosis*) requires a cross-sectional epistemology that participates in the philosophy of care, ethics and subjectivation of the person with ED, and confer a symbolic value on the symptom
- The desperate quest and the catholic mystic value of the "anorexic cry", the implication of health sciences, and the nature of concepts derived from humanities are related and link the anorexic subject and the system of care to the Sacred.

We suggest that transdisciplinarity, *via* the disappearance of boundaries, promotes an open dialogue between the somatic, psychiatric, nutritional and human science approaches. Transdisciplinary practice, requiring a very strong disciplinary identity, contributes to the evolution and the creativity of the different disciplines, and to the development of common skills and culture (knowledge, concepts, tools, methods, epistemological contributions). Concerning the patient with an ED, transdisciplinarity provides a global approach in a "totalizing and unifying" view, which might be beneficial to the subject's experience and to the outcome of symptoms. The wide variety of knowledge and skills from multiple disciplines, the conflicting timeframes of the *somatic* or *psychological* practices, the redistribution of responsibilities, and fantasies of omniscience and omnipotence generated by the sharing of knowledge, could all be real drawbacks for professionals dealing with patients affected by an ED in a multi-professional space. Without transdisciplinarity, these barriers could foster the inter-professional conflicts and induce vulnerability feelings for caregivers, such

as professional identity issues and role confusion when dealing with both physical and psychological problems in a patient with an ED. Advantages and drawbacks of transdisciplinary approach for the patient and for the professionals need to be assessed. In terms of research, transdisciplinarity in the ED field should encourage innovation and creation, opening up new lines of thought, and it should promote the development of research projects that cannot be achieved by the mono-, multi- or interdisciplinary approaches. The methodological approach and its scientific validity but also the evaluation criteria of transdisciplinary research have to be carefully specified.²⁰

At the beginning of the 21st century, transdisciplinarity in the area of ED appears as an epistemological break, an open dialogue gathering diverse school of thought and leading them to evolve. Transdisciplinarity, a concept of the "hypermodern era", reconciling medical theory and practice, is an innovative model for a humanistic and integrative approach for adolescent and young adults with ED and healthcare teams, and it encourages new methodologies for research. While transdisciplinarity seems essential to understand the current organization of care and research in eating disorders, an ensuing theoretical modeling of the transdisciplinarity is now required. This presents a challenging perspective for researchers working in the ED field.

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DISCUSSION

DISCUSSION

Ce travail de thèse a été initié par un mouvement personnel de l'auteure passant d'une discipline académique à un environnement où les disciplines appartenant à des champs épistémologiquement distincts étaient convoquées, par nécessité, pour accueillir la souffrance adolescente (Moro, 2012 ; Perret, et al., 2012). La mise en commun des compétences et des savoirs multiples tendaient donc vers un seul et même objectif qui était celui d'accueillir la complexité de la souffrance adolescente et plus particulièrement, en ce qui concerne notre domaine d'étude, vers un objet complexe qui est l'adolescent souffrant de TCA (Benoit, et al., 2011 ; Blanchet-Collet, et al., 2013).

Nous avons montré au travers des trois articles présentés, que la transdisciplinarité était légitime et pertinente pour décrire le champ des TCA, mais également que la recherche transdisciplinaire avait des applications dans le domaine de la compréhension et du soin apportés aux patients souffrant de TCA. Nous proposons donc d'organiser notre discussion autour de trois thèmes principaux :

- la transdisciplinarité dans le champ des TCA : une nouvelle épistémologie, un nouvel espace de pensée
- la transdisciplinarité dans le champ des TCA : une nouvelle pratique clinique
- la transdisciplinarité dans le champ des TCA : une nouvelle méthodologie pour la recherche.

Nous terminerons notre discussion par les perspectives de l'approche transdisciplinaire dans le champ des TCA.

I. La transdisciplinarité dans le champ des TCA : une nouvelle épistémologie, un nouvel espace de pensée

L'espace institutionnel où se jouent ces rencontres, "entre, à travers et au-delà" les frontières des disciplines, peut être considéré comme un "environnement thérapeutique" au sens de Winnicott (Houssier, 2019), permettant d'assurer l'accueil et le "holding" des adolescents souffrant de TCA mais représente également une unité de lieu propice au développement de la pensée transdisciplinaire. Cette pensée transdisciplinaire ne naît pas *ex nihilo* du regroupement de professionnels provenant d'horizons variés dans une même unité de lieu, mais nécessite la volonté et la capacité des équipes à créer une culture commune en partageant connaissances théoriques, savoirs, outils et méthodologies; ce sont à ces conditions réunies que peuvent naître la pensée et la pratique transdisciplinaires. Cela revient, dans la pratique institutionnelle à faire non seulement se croiser mais plus largement, comme c'est le cas dans une Maison des Adolescents, à faire cohabiter plusieurs types de cultures et notamment, pour évoquer les quatre champs disciplinaires à l'oeuvre dans l'espace TCA, les cultures disciplinaires médicales entre elles, mais également les cultures médicales avec les sciences humaines.

C'est bien là l'une des particularités de l'objet TCA que de convier avec autant de vigueur les disciplines médicales et les sciences humaines, et d'en favoriser le dialogue au-delà des obstacles épistémologiques (Nicolescu, 2011). L'objet anorexique, et plus largement tous les TCA, nécessite en effet à la fois le haut niveau de preuves médicales et d'objectivité scientifique apportés par la médecine et les sciences exactes, et le regard subjectivant des sciences humaines porté sur le patient et sur le soignant. Ces différents regards apportent des éclairages qui loin de s'exclure se complètent, se croisent, interagissent et participent à enrichir l'objet anorexique favorisant la progression des approches en pratique clinique, des modèles de compréhension en recherche mais aussi, de l'épistémologie des "figures anorexiques" de l'ère transdisciplinaire. Ainsi, l'objet

anorexique, par sa singularité, parvient à convoquer les disciplines et les différents protagonistes impliqués dans le champ TCA, à les maintenir rassemblés et à les faire évoluer. La construction des échanges transdisciplinaires dans le champ TCA doit s'appuyer sur des ancrages disciplinaires forts mais également sur l'existence d'alliances naturelles historiquement créées entre des disciplines partageant une épistémologie commune comme la médecine somatique et la nutrition, ou la psychiatrie et la psychologie. Le niveau d'intégration, correspondant à l'incorporation de concepts d'autres disciplines, est en effet étroitement lié à la proximité épistémologique des disciplines concernées (Nissani, 1995). La participation dans le champ TCA de certaines disciplines fondées sur une approche naturellement intégrative, comme celle inhérente à la pratique de la médecine de l'adolescent (Alvin, 2007 ; Lefèvre, Blanchet, Cosson, Mimoun, & Ferrand, 2008) semble favoriser indéniablement la dialectique disciplinaire.

Si la complexité de l'objet TCA sollicite *de facto* les médecines somatiques et psychiatriques, permettant de dépasser le clivage corps-esprit, elle interroge sinon la totalité, la majorité des champs des sciences humaines. Qu'elles s'attardent spécifiquement au chevet des TCA, en accordant une valeur symbolique au symptôme (engagement anorexique, élitisme revendiqué, inversion des rapports de domination...) par l'apport de modèles sociologiques (Darmon, 2003), anthropologiques (Tinat, 2008), ou psychanalytiques (Raimbault, & Éliacheff, 1996 ; Maître, 2000), ou qu'elles abordent la question du sujet en santé (Canguihlem, 2002 ; Foucault, 2015 ; Klein, 2014) les sciences humaines participent à rendre sa dignité et son humanité au sujet souffrant de TCA. Les différents témoignages contemporains issus de la littérature "faminine" (Meuret, 2006), ou véhiculés par d'autres médias, participent également à enrichir le savoir et la culture commune et influencent l'évolution des disciplines et des différents acteurs qui composent le champ des TCA. Par ailleurs, nous suggérons que les contributions épistémologiques des "figures anorexiques" et des "approches collectives" qui participent à la construction de la philosophie du soin et du cadre thérapeutique actuel, permettent de développer une pensée

influencée par une culture commune “entre, à travers, et au-delà” des frontières disciplinaires qui favorise les échanges transdisciplinaires dans le champ TCA. Ces figures anorexiques qui, traversant dans une “lignée matrilineaire” les âges et le temps, viennent interpeller les différentes disciplines et professionnels qui s’attardent, comme les badauds devant la cage de “l’artiste du jeûne” (Kafka, 1995), à la fois intrigués, fascinés, déconcertés par l’entêtement, la détermination à mort de ces jeunes patient(e)s. Chacun tentant d’en trouver la clef et d’apporter, en l’ignorant le plus souvent, sa pierre à l’édifice de la pensée transdisciplinaire.

Ainsi, la pensée transdisciplinaire dans le champ des TCA, est une pensée intégrant les connaissances théoriques, concepts et outils des disciplines et partenaires en interaction, nourrie également du savoir collectif issu des sciences humaines et des contributions épistémologiques des figures anorexiques et des approches collectives. Cette pensée est également alimentée et renouvelée par les relations intersubjectives entre le sujet malade et les différents protagonistes du système complexe précédemment décrit. Concernant le cheminement de l’auteure, le passage de la pensée disciplinaire à la pensée transdisciplinaire s’est construit, au fil de sa trajectoire, à l’occasion de rencontres successives avec un objet complexe et des environnements complexes. La construction de l’identité professionnelle est un long processus évolutif et cognitif qui se construit à partir d’éléments expérimentaux nourris d’interactions avec l’objet et les différents protagonistes. Dans le cadre de la pratique transdisciplinaire, il semble que l’intégration des concepts et de savoirs issus de multiples disciplines, et dans notre cas, des contributions épistémologiques multiples, participe à l’évolution de la pensée disciplinaire vers une pensée plus complexe. La lente transformation de la pensée et de soi s’opère par différents mécanismes d’échanges avec le patient souffrant de TCA, par la confrontation au savoir diffusé par d’autres disciplines (pour l’auteure par les disciplines psychiatriques, la psychologie, les sciences humaines) mais également par les différents protagonistes du système complexe des TCA. La capacité d’évolution du mode de pensée des acteurs impliqués dans le champ

TCA dépendrait de leur "perméabilité" à se laisser traverser par les différentes perspectives disciplinaires. Nous suggérons que le parcours "initiatique" de chaque acteur, comme cela fut le cas pour l'auteure, favorise la "perméabilité" au savoir et aux outils qui circulent "entre, au travers et au-delà" les frontières de l'espace transdisciplinaire. C'est ainsi que la pensée disciplinaire évolue vers la pensée transdisciplinaire, qui autorise une modification progressive des pratiques, générant à leur tour une modification des interactions réciproques avec l'objet permettant ainsi de faire évoluer la philosophie et le cadre de soin. En y regardant de plus près, c'est cela que nous enseignent l'épistémologie des figures anorexiques et celle des approches collectives. Du point de vue purement individuel, nous pouvons considérer que l'acteur qui "au travail" dans le champ transdisciplinaire auprès des patients souffrant de TCA, est lui-même détenteur d'un savoir transdisciplinaire, qu'il peut utiliser dans sa pratique clinique et de recherche dans une position métadisciplinaire (Létourneau, 2010). La pensée transdisciplinaire est une pensée sollicitante et exigeante, fondée sur des connaissances objectives (*épistémè*) ou savoir du dehors (théories scientifiques, dogmes, connaissances acquises) associé à un savoir du dedans (*gnose*) (imagination active, intuition, émotions, spiritualité ...). C'est en cela que Nicolescu distingue le savoir théorique associé à la connaissance disciplinaire de la compréhension associée à la connaissance transdisciplinaire (Nicolescu, 2011), précisant que la compréhension transdisciplinaire intègre des valeurs humanistes et que "sa finalité est la compréhension du monde présent". La pensée transdisciplinaire autorise une vision "unifiante, englobante de la Réalité, sans jamais l'épuiser entièrement" (Nicolescu, 1993). Elle permet ainsi de saisir ce que la pensée monodisciplinaire dogmatique ne peut saisir, nécessitant l'effort de s'extraire de sa "cage dorée" (Bruch, 1962) pour accéder à un espace de pensée plus chaotique, qui caractérise la pensée complexe (Morin, 2005). La pensée transdisciplinaire opérant à un haut niveau de complexité et donc de plus faible certitude, est une pensée libre, indisciplinée, en renouvellement continu, alimentée par les interactions et les courants qui traversent le sujet "entre, au travers, et au-delà" de ses frontières internes. C'est la complexité et la richesse de

cette pensée, reposant sur les trois postulats que sont “les niveaux de réalité, la logique du tiers inclus, et la complexité” précédemment décrits (Nicolescu, 1996) qui permettent d’accéder aux différents niveaux de réalité et à la complexité de l’objet TCA et de construire une pratique singulière et créative auprès de ces patients rendant compte des progrès considérables réalisés dans les soins et la recherche dans le champ TCA au cours de ces dernières années.

II. La transdisciplinarité dans le champ des TCA : une nouvelle pratique clinique

Dans le domaine du soin avec les patients adolescents souffrant de TCA, la nécessaire approche transdisciplinaire est une pratique passionnante mais exigeante en raison du haut niveau de complexité de l’objet et de la vertigineuse multitude des interactions, venant bouleverser les identités des disciplines et possiblement celles des différents acteurs impliqués dans le système de soin. Comme le suggère Edgar Morin : “en ce qui concerne la transdisciplinarité, il s’agit souvent de schèmes cognitifs qui peuvent traverser les disciplines, parfois avec une virulence telle qu’elle les met en transe” (Morin, 1994). Les protagonistes intervenant dans ce système de soin complexe doivent partager un mode de pensée qui intègre et dépasse les perspectives individuelles de chaque professionnel permettant dans la pratique clinique autour de l’objet anorexique d’appréhender la “santé globale” de “l’homme global” (Paul, 2007) et d’en acquérir une vision totalisante et unifiante. La pratique transdisciplinaire est “une audace au niveau personnel, car cela implique l’engagement envers sa propre transformation et ses propres apprentissages, tout en prenant conscience de ses propres contradictions” (Gonzales, 2014).

La pratique transdisciplinaire, s’appuyant sur les postulats de la transdisciplinarité qui sont les niveaux de réalité, la logique du tiers inclus et la complexité, se révèle particulièrement légitime pour accueillir, à tous les niveaux de sa prise en charge, le patient souffrant d’un TCA et ses paradoxes. Néanmoins, l’approche transdisciplinaire ne doit pas être exclusive des autres approches, et doit s’associer et inclure les autres modalités d’action ou d’interaction

disciplinaires (intra-, mono-, pluri-, interdisciplinaire) notamment dans les étapes initiales de la prise en charge ou dans des situations aiguës (urgences somatiques ou psychiatrique ou environnementales). Par ailleurs, dans le cadre de l'approche transdisciplinaire, d'autres modalités d'interactions disciplinaires participent à la formation et à l'évolution du savoir individuel des professionnels et à l'enrichissement des disciplines (égo-interdisciplinarité, circum-disciplinarité, cross-disciplinarité). Il nous semble également nécessaire d'envisager que différents niveaux d'intensité de pratique transdisciplinaire puissent être convoqués par des situations à haut niveau de complexité pouvant mettre en difficultés les équipes soignantes. Il convient de repérer les situations hautement complexes justifiant le recours à un "haut niveau" de pensée transdisciplinaire qui permettra la mise en place de propositions thérapeutiques créatives ne trouvant pas d'issue dans une approche transdisciplinaire "classique". Nous illustrons notre propos par une série de situations à haut niveau de complexité justifiant un haut niveau d'intensité de la pratique transdisciplinaire : les formes résistantes de TCA, les TCA associant de multiples comorbidités dans les champs somatique, psychiatrique et psychosocial, les TCA dans le champ transculturel, les prescriptions médicamenteuses "hors pratique courante" chez l'adolescent TCA (les traitements substitutifs en hormones sexuelles; l'hormone de croissance ; les thymorégulateurs chez l'adolescent ; les stimulations cérébrales...); les TCA et les dysphories de genre ; les TCA et le processus de transition ; les TCA et l'éducation thérapeutique ; les TCA et les soins sous contraintes ; les TCA et les soins palliatifs. Cette liste non exhaustive s'inspire de situations cliniques vécues au cours de notre pratique institutionnelle et d'activité de réseau.

Si la pratique transdisciplinaire est associée au partage des connaissances et des outils et participe de l'enrichissement individuel et disciplinaire, elle vient également questionner les rôles et les savoirs de chacun des acteurs, posant ainsi les limites de leurs compétences (de La Tribonnière, & Gagnayre, 2011). Ainsi, si les bénéfices de la pratique transdisciplinaire pour l'objet et les disciplines semblent établis, il nous apparaît légitime de nous questionner sur les

modifications induites chez les professionnels qui la pratiquent. La remise en question des identités professionnelles peut être un facteur de vulnérabilité potentielle pour les individus et les équipes engagées dans ce système complexe. Les équipes prenant en charge les patients souffrant de TCA dans un système transdisciplinaire comme notre environnement institutionnel, doivent intégrer deux niveaux de difficultés spécifiques qui correspondent au phénomène de “release” et de “role expansion” (Choi, & Pak, 2006, p355). Le phénomène de “release” consiste à lâcher prise en acceptant qu’un professionnel d’une autre discipline puisse effectuer une tâche qui relève de sa propre spécialité (par exemple, dans le cas de l’auteure accepter que le psychiatre parle des modalités de renutrition...), et nous ajouterons de comprendre que la perspective de cette autre discipline puisse apporter un nouvel éclairage et ouvrir d’autres possibles pour le patient. A l’inverse, le phénomène de “role expansion” revient à accepter de prendre à son compte des actes qui sont du ressort d’une autre discipline (par exemple, dans le cas de l’auteure évoquer avec un adolescent souffrant de TCA l’intérêt des psychotropes dans cette pathologie...). Ainsi, dans le champ des TCA chaque acteur doit garder son ancrage et son identité disciplinaire tout en acceptant que le rôle de chacun des acteurs soit, à l’image de la pensée transdisciplinaire, un rôle hybride dont les contours sont parfois difficiles à décrire. La pratique transdisciplinaire nécessite et doit favoriser la mise en place de dispositifs institutionnels et de travail de supervision, incluant l’apport épistémologique des sciences humaines, permettant aux professionnels d’accéder à d’autres niveaux de pensée complexe. Cet accompagnement des pratiques soignantes nous semble essentiel d’une part à visée réflexive, permettant aux professionnels de mieux appréhender ce qui les traverse et ce savoir hybride qu’ils détiennent, mais également pour aider le regard soignant confronté au patient souffrant de TCA à “regarder au-delà du visible” (Foucault, 2015) et aborder des questions centrales dans l’accompagnement de ces patients que sont:

- les représentations de la maladie et la valeur symbolique du symptôme anorexique et des autres TCA

- la complexité de l'objet anorexique, ses résistances, ses ambivalences, et les mouvements d'agressivité projetés dont on ne doit pas sous-estimer l'impact sur l'équipe
- l'engagement professionnel transdisciplinaire en tant que "travail collectif sur la personne" qui vise à accompagner le patient dans un désengagement anorexique et à trouver de "nouvelles dispositions" (Darmon, 2003)
- les relations intersubjectives (subjectivités médicales, soignantes ou du patient).

Aussi, à la lumière de notre expérience, nous suggérons que toute équipe souhaitant développer une compétence et construire une pratique dans le champ des TCA se forme à la connaissance de la transdisciplinarité, son cadre théorique, ses enjeux (bénéfices et risques) et ses nombreuses applications.

III. La transdisciplinarité dans le champ des TCA : une nouvelle méthodologie pour la recherche

Comme précédemment décrit, la recherche transdisciplinaire s'est développée en France, et dans d'autres pays du monde, il y a une vingtaine d'année sous l'impulsion du CIRET. Nous débiterons donc cette dernière partie de notre discussion en rappelant le contenu de la déclaration de Venise (1986) :

- "(...) nous reconnaissons (...) l'urgence d'une recherche véritablement transdisciplinaire dans un échange dynamique entre les sciences "exactes", les sciences "humaines", l'art et la tradition. Dans un sens, cette approche transdisciplinaire est inscrite dans notre propre cerveau par l'interaction dynamique entre ses deux hémisphères. L'étude conjointe de la nature et de l'imaginaire, de l'univers et de l'homme, pourrait ainsi mieux nous approcher du réel et nous permettre de mieux faire face aux

différents défis de notre époque“²².

Parmi la centaine de thèses de doctorat recensées entre 1992 et 2018 par le Centre International de Recherches Transdisciplinaires (CIRET) aucune n'est en lien avec la pratique médicale et encore moins avec le pratique médicale qui concerne les patients souffrant de TCA. Dans le champ des TCA, la recherche transdisciplinaire reste insuffisamment développée en France et plus largement en Europe. Elle apparaît pourtant particulièrement adaptée à la complexité de l'objet et à la complexité du champ pratique et théorique des TCA. La recherche transdisciplinaire s'est récemment construite, au cours de ces dernières années, autour d'initiatives locales institutionnelles et a pu se fédérer plus largement au travers de rencontres de professionnels de différentes disciplines médicales et de chercheurs fondamentaux avec la création d'un groupe de recherche transdisciplinaire dans le cadre de la FFAB qui a donné lieu à différents travaux récents impliquant l'auteure (Gorwood, et al., 2016 ; Blanchet, et al., 2019).

Il nous semble souhaitable d'opérer une distinction entre la recherche transdisciplinaire (utilisant la méthodologie transdisciplinaire) et la recherche sur la transdisciplinarité (utilisant possiblement différentes méthodologies). Concernant le cadre précis de notre objet, il serait très tentant de faire l'amalgame entre les deux types de recherches, l'objet TCA étant par définition transdisciplinaire. Ainsi, on pourrait envisager à tort, que l'ensemble des recherches menées dans un cadre transdisciplinaire, autour d'un objet transdisciplinaire soient transdisciplinaires. Comme nous en avons précédemment débattu autour de la pratique transdisciplinaire, il nous apparaît essentiel de pouvoir mener parallèlement à la recherche transdisciplinaire des recherches mono, pluri ou interdisciplinaires autour de l'objet de notre choix, et ceci précisément dans des contextes où notre questionnement concerne un aspect très spécialisé sollicitant un haut niveau d'expertise disciplinaire.

²² Citation disponible dans son intégralité sur le site du CIRET (www.ciret-transdisciplinarity.org)

La méthodologie de la recherche transdisciplinaire s'appuie sur les trois postulats de base de la transdisciplinarité qui sont les niveaux de réalité, la logique du tiers inclus et la complexité. La recherche transdisciplinaire est destinée d'une manière générale aux questions qui se situent "entre, au travers et au-delà" les frontières disciplinaires, qui par définition ne pourraient être résolues dans le cadre d'une recherche disciplinaire. A l'inverse, certaines questions se situant dans le cadre strictement disciplinaire ne justifient pas, voir contre-indiquent le recours à une démarche transdisciplinaire. Ainsi, le choix de l'objet, de l'objectif et du terrain de recherche sont des éléments centraux dans l'élaboration d'un projet de recherche transdisciplinaire (Le Boulch, 2002) et déterminent le choix de la méthodologie. L'une des difficultés de la recherche transdisciplinaire est la multiplicité des outils de recherche disponibles et des méthodes propres à chaque discipline, justifiant un choix rigoureux de la méthodologie et de son cadre scientifique sous peine de voir son travail invalidé par manque de rigueur scientifique. Dans le champ des TCA, les méthodes mixtes intégrant outils de recherche qualitative et quantitative semblent particulièrement adaptées pour explorer les différents niveaux de réalité de l'objet. Une autre difficulté de la recherche transdisciplinaire qui nous est apparue au cours de notre travail est le risque de confondre l'objectif et les moyens, et que le chercheur transdisciplinaire se laisse dévier de son objectif par la richesse des champs explorés et la nécessaire créativité et intuition associées à la mise en œuvre de la pensée transdisciplinaire. Enfin, s'éloignant du cadre disciplinaire d'origine, la reconnaissance du chercheur transdisciplinaire par ses pairs peut s'avérer délicate, de même que la valorisation du travail de recherche transdisciplinaire confrontée à plusieurs obstacles qui concernent le langage utilisé lors de l'écriture ainsi qu'au public à laquelle elle s'adresse, autrement dit au choix des revues, des colloques et autres contextes de communication.

Les travaux de recherche transdisciplinaire dans le champ des TCA peuvent prendre comme objet tous les acteurs impliqués dans le système précédemment décrit et peuvent concerner l'épidémiologie, le diagnostic, la clinique, les modèles explicatifs, les dispositifs de soin ou les modalités thérapeutiques

autour de "l'objet TCA". La recherche transdisciplinaire, en miroir de ce que nous avons évoqué autour de la pratique clinique, ne se résume pas à réunir des chercheurs de disciplines différentes autour d'un objet. Elle requiert un déploiement d'énergie considérable pour "faire l'effort" de la pensée complexe, dans le choix de l'objet et des objectifs à atteindre ainsi que des moyens pour y parvenir. C'est à ce prix que la recherche transdisciplinaire pourrait se révéler indispensable pour aborder les questions les plus complexes rencontrées dans le champ des TCA, et devrait permettre d'apporter des réponses innovantes et créatives dans le domaine de la compréhension et du soin pour les patients souffrant de TCA.

CONCLUSION et PERSPECTIVES

Notre travail, résultant d'une trajectoire individuelle singulière, qui nous a conduit à nous intéresser à un objet transdisciplinaire dans un environnement qui l'est tout autant, a répondu à plusieurs objectifs fixés.

Le premier objectif était de découvrir le concept de transdisciplinarité et de le relier au système complexe que représente l'espace pratique et théorique des TCA, que nous avons désigné par "champ des TCA". Nous avons pu confirmer la légitimité et la pertinence de ce concept pour décrire le champ des TCA, qui s'impose au 21^{ème} siècle à la fois comme une rupture épistémologique, une nouvelle position intellectuelle et un espace de pensée hybride et intégrative rassemblant les différents savoirs disciplinaires et leur permettant d'évoluer.

Le second objectif a été de présenter, au travers de nos travaux de recherche transdisciplinaires, des applications dans le domaine de la compréhension par la construction d'un modèle explicatif transdisciplinaire, et dans le domaine du soin par une approche transdisciplinaire des approches médicamenteuses de l'anorexie mentale. Cette partie de notre travail nous montre que la pensée transdisciplinaire représente un remarquable changement paradigmatique permettant une approche innovante et créative, proposant une vision unifiante

et totalisante, adaptée à la complexité de l'objet anorexique, et que nous pensons, de façon plus générale, applicable à tout type de TCA.

Enfin, nous avons amorcé une proposition de modélisation de la transdisciplinarité dans le champ des TCA, mais ce projet ambitieux s'est heurté au choix des bases théoriques et à au temps dont nous disposons. Nous poursuivrons ce travail dans nos différents champs (soins, recherche).

Le mouvement initié par notre travail qui a permis la rencontre de la pensée complexe et la découverte d'un concept, la transdisciplinarité, idéalement adapté à l'objet TCA et à notre environnement de travail, a fait émerger le désir de conduire d'autres travaux, dont nous présentons les axes principaux :

- Modéliser le champ TCA de manière plus fine. Le choix des bases théoriques semble s'orienter vers la théorie générale des systèmes (Von Bertalanffy, 2012)
- Construire une approche réflexive sur les mécanismes à l'œuvre dans l'évolution de notre pensée et la transformation de notre pratique dans le champ TCA
- Évaluer les représentations de la pathologie TCA et des soins par les patients, familles et soignants dans un contexte de soin transdisciplinaire (travail en cours)(méthodologie qualitative)
- Évaluer les pratiques individuelles et institutionnelles (pratiques du travail) et l'expérience subjective des soignants dans un dispositif de soin transdisciplinaire (méthodologie qualitative) autour de l'objet TCA.

Ces projets feront l'objet d'études ultérieures et viendront prolonger notre approche théorique par des données empiriques, permettant de faire évoluer les pratiques au service du patient adolescent souffrant de TCA, tout en prenant en compte les besoins individuels et institutionnels.

Ainsi, la transdisciplinarité, apparaît comme un concept innovant dans le champ des TCA à l'adolescence, réconciliant théorie et pratique, et rappelant, si

besoin en était, la place des sciences humaines aux côtés des disciplines médicales dans l'approche de ces troubles complexes et sévères. La transdisciplinarité confère un nouveau cadre éthique au sujet souffrant de TCA, un nouveau savoir et un nouveau mode de pensée hybride et créatif aux acteurs impliqués, ainsi que de nouvelles perspectives d'application dans le domaine du soin, de la recherche (et de l'enseignement). Plus largement, nous suggérons que ce modèle puisse être appliqué aux autres types de TCA et à d'autres catégories d'âge ou de genre. Si la transdisciplinarité, peut être considérée comme une flèche supplémentaire à "l'arc de la connaissance" médicale, nous pensons que ce modèle, pour être appliqué, déployé et scientifiquement reconnu et enseigné, nécessite une forme de liberté et d'indisciplinarité dans un environnement institutionnel et un contexte sociopolitique qui doivent être sensibilisés à ces questions.

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ANNEXES



1970 : Conférence de l'OCDE à Nice-France 7-12 Septembre 1970 intitulée "L'interdisciplinarité - Problèmes d'enseignement et de recherche dans les universités"; naissance du concept de Transdisciplinarité par Jean Piaget (PIAGET, 1972)

1986 : Colloque de Venise sous l'égide de l'UNESCO : "promouvoir une réflexion dirigée vers la transdisciplinarité et l'universalité"

1987 : Centre International de Recherches et Etudes Transdisciplinaires (CIRET, Paris) : association régie par loi 1901, président Basarab NICOLESCU

1994 : - Premier Congrès Mondial de la Transdisciplinarité à Convento da Arrábida-Portugal 2-7 Novembre 1994 (de Freitas, Morin, & Nicolescu, 1994) ; la conférence inaugurale d'E. Morin : "Transdisciplinarité et complexité" (cité par VALLADE, p87, 2013)

- Charte de la transdisciplinarité: "un ensemble de principes fondamentaux de la communauté des esprits transdisciplinaires, constituant un contrat moral que tout signataire de cette charte fait avec soi-même, en dehors de toute contrainte juridique et institutionnelle" (ANNEXE II)

1996 : La Transdisciplinarité-Manifeste (NICOLESCU, 1996)

1997 : Congrès de Locarno, Suisse (30 avril - 2 mai 1997) CIRET-UNESCO : "Déclaration et recommandations- Quelle université pour demain ?" (CIRET) ; André Bourguignon, médecin psychanalyste prononçait sa célèbre conférence sur la transdisciplinarité (BOURGUIGNON, 1997).

2005 : Deuxième Congrès Mondial de la Transdisciplinarité à Vitoria-Bésil, 2-9 septembre 2005)

2008 : Transdisciplinarity - Theory and Practice (sous la direction de Basarab Nicolescu), Hampton Press, USA, 2008

2018 : The ATLAS International Transdisciplinary-Transnational-Transcultural (T3) Conference "Being Transdisciplinary" (Babes-Bolyai University, Cluj-Napoca, Romania (3-7 Juin, 2018)

2019 : Florent PASQUIER actuel Président du CIRET

ANNEXE I: étapes fondatrices dans l'histoire de la transdisciplinarité- *adapté par l'auteur à partir de l'historique disponible sur le site du CIRET www.ciret-transdisciplinarity.org*

Charte de la transdisciplinarité

Centre international de recherches et études transdisciplinaires.

Adoptée au premier congrès mondial de la Transdisciplinarité, Convento da Arrábida, Portugal, 2-6 novembre 1994.

Comité de rédaction :
Lima de Freitas,
Edgar Morin et
Basarab Nicolescu.

Préambule

Considérant que la prolifération actuelle des disciplines académiques et non-académiques conduit à une croissance exponentielle du savoir ce qui rend impossible tout regard global de l'être humain,

Considérant que seule une intelligence qui rend compte de la dimension planétaire des conflits actuels pourra faire face à la complexité de notre monde et au défi contemporain d'autodestruction matérielle et spirituelle de notre espèce,

Considérant que la vie est lourdement menacée par une technoscience triomphante, n'obéissant qu'à la logique effrayante de l'efficacité pour l'efficacité,

Considérant que la rupture contemporaine entre un savoir de plus en plus accumulatif et un être intérieur de plus en plus appauvri mène à une montée d'un nouvel obscurantisme, dont les conséquences sur le plan individuel et social sont incalculables,

Considérant que la croissance des savoirs, sans précédent dans l'histoire, accroît l'inégalité entre ceux qui les possèdent et ceux qui en sont dépourvus, engendrant ainsi des inégalités croissantes au sein des peuples et entre les nations sur notre planète,

Considérant en même temps que tous les défis énoncés ont leur contrepartie d'espérance et que la croissance

extraordinaire des savoirs peut conduire, à long terme, à une mutation comparable au passage des hominiens à l'espèce humaine,

Considérant ce qui précède, les participants au premier congrès mondial de Transdisciplinarité (Convento da Arrábida, Portugal, 2-7 novembre 1994) adoptent la présente *Charte* comprise comme un ensemble de principes fondamentaux de la communauté des esprits transdisciplinaires, constituant un contrat moral que tout signataire de cette *Charte* fait avec soi-même, en dehors de toute contrainte juridique et institutionnelle.

Article 1

Toute tentative de réduire l'être humain à une définition et de le dissoudre dans des structures formelles, quelles qu'elles soient, est incompatible avec la vision transdisciplinaire.

Article 2

La reconnaissance de l'existence de différents niveaux de réalité, régis par des logiques différentes, est inhérente à l'attitude transdisciplinaire. Toute tentative de réduire la réalité à un seul niveau régi par une seule logique ne se situe pas dans le champ de la transdisciplinarité.

Article 3

La transdisciplinarité est complémentaire de l'approche disciplinaire ; elle fait émerger de la confrontation des disciplines de nouvelles données qui les articulent

entre elles ; et elle nous offre une nouvelle vision de la nature et de la réalité. La transdisciplinarité ne recherche pas la maîtrise de plusieurs disciplines, mais l'ouverture de toutes les disciplines à ce qui les traverse et les dépasse.

Article 4

La clef de voûte de la transdisciplinarité réside dans l'unification sémantique et opérative des acceptions *à travers* et *au-delà* des disciplines. Elle présuppose une rationalité ouverte, par un nouveau regard sur la relativité des notions de « définition » et d'« objectivité ». Le formalisme excessif, la rigidité des définitions et l'absolutisation de l'objectivité comportant l'exclusion du sujet conduisent à l'appauvrissement.

Article 5

La vision transdisciplinaire est résolument ouverte dans la mesure où elle dépasse le domaine des sciences exactes par leur dialogue et leur réconciliation non seulement avec les sciences humaines mais aussi avec l'art, la littérature, la poésie et l'expérience intérieure.

Article 6

Par rapport à l'interdisciplinarité et à la multidisciplinarité, la transdisciplinarité est multiréférentielle et multidimensionnelle. Tout en tenant compte des conceptions du temps et de l'histoire, la transdisciplinarité n'exclut pas l'existence d'un horizon transhistorique.

Article 7

La transdisciplinarité ne constitue ni une nouvelle religion, ni une nouvelle philosophie, ni une nouvelle métaphysique, ni une science des sciences.

Article 8

La dignité de l'être humain est aussi d'ordre cosmique et planétaire. L'apparition de l'être humain sur la Terre est une des étapes de l'histoire de l'Univers. La reconnaissance de la Terre comme patrie est un des impératifs de la transdisciplinarité. Tout être humain a droit à une nationalité, mais, au titre d'habitant de la Terre, il est en même temps un être transnational. La reconnaissance par le droit international de la double appartenance - à une nation et à la Terre - constitue un des buts de la recherche transdisciplinaire.

Article 9

La transdisciplinarité conduit à une attitude ouverte à l'égard des mythes et des religions et de ceux qui les respectent dans un esprit transdisciplinaire.

Article 10

Il n'y a pas un lieu culturel privilégié d'où l'on puisse juger les autres cultures. La démarche transdisciplinaire est elle-même transculturelle.

Article 11

Une éducation authentique ne peut privilégier l'abstraction dans la connaissance. Elle doit enseigner à contextualiser, concrétiser et globaliser. L'éducation transdisciplinaire réévalue le rôle de l'intuition, de l'imaginaire, de la sensibilité et du corps dans la transmission des connaissances.

Article 12

L'élaboration d'une économie transdisciplinaire est fondée sur le postulat que l'économie doit être au service de l'être humain et non l'inverse.

Article 13

L'éthique transdisciplinaire récuse toute attitude qui refuse le dialogue et la discussion, quelle que soit son origine - d'ordre idéologique, scientiste, religieux, économique, politique, philosophique. Le savoir partagé devrait mener à une compréhension partagée fondée sur le respect absolu des altérités unies par la vie commune sur une seule et même Terre.

Article 14

Rigueur, *ouverture* et *tolérance* sont les caractéristiques fondamentales de l'attitude et de la vision transdisciplinaires. La *rigueur* dans l'argumentation qui prend en compte toutes les données est le garde-fou à l'égard des dérives possibles. L'*ouverture* comporte l'acceptation de l'inconnu, de l'inattendu et de l'imprévisible. La *tolérance* est la reconnaissance du droit aux idées et vérités contraires aux nôtres.

Article final

La présente *Charte de la Transdisciplinarité* est adoptée par les participants au premier congrès mondial de Transdisciplinarité, ne se réclamant d'aucune autre autorité que celle de leur œuvre et de leur activité.

Selon les procédures qui seront définies en accord avec les esprits transdisciplinaires de tous les pays, la Charte est ouverte à la signature de tout être humain intéressé par les mesures progressives d'ordre national, international et transnational pour l'application de ses articles dans la vie.

Convento da Arrábida, le 6 novembre 1994. ■