Management of first depression or generalized anxiety disorder episode in adults in primary care: A systematic metareview

Damien Driot 1,2, Michel Bismuth 2, Adrien Maurel 1, Julie Soulie-Albouy 2, Jordan Birebent 2, Stéphane Oustric 1,2, Julie Dupouy 1,2

Available online:
1. University Toulouse III, UMR 1027 Inserm, 37, allées Jules-Guesde, 31000 Toulouse, France
2. University Toulouse III, General Practice Department, 133, route de Narbonne, 31062 Toulouse cedex, France

Correspondence:
Damien Driot, UMR 1027 Inserm, 37, allées Jules-Guesde, 31400 Toulouse, France.
damien.driot@univ-tlse3.fr

Summary

Context > General Practitioners (GPs) are the leading antidepressants prescribers in Europe and in France. Difficulties in implementing existing recommendations in daily practice have been described.

Objective > The objective of this study was to elaborate two algorithms to guide GPs in the patient management for a first major depressive disorder (MDD) or generalized anxiety disorder (GAD) episode in primary care.

Data sources > PubMed, Cochrane, and ISI Web of Science were explored using mainly the following keywords: depressive disorder, anxiety disorders, antidepressive agents or antidepressant. PubMed was explored using Medical Subject Headings (MeSH). Grey literature was also considered through the analysis of articles references, congress publications, guidelines and clinical practice recommendations.

Study selection > A systematic meta-review (overview of reviews) including systematic reviews, meta-analyses, guidelines and clinical practice recommendations, published from January 2002 to December 2015, was performed. The methodological and report qualities were assessed by the AGREE II, PRISMA checklist and R-AMSTAR grid. Each step was performed independently by two researchers following a process derived from the PRISMA statement. A narrative synthesis on main clinical data to collect before prescription in primary care, key information for patients, and recommended follow-up was realized.

Results > Thirty articles were included: 11 meta-analyses, 19 guidelines. For moderate to severe MDD, selective serotonin reuptake inhibitors (SSRI) should be associated with psychotherapy (cognitive behavioral therapy). For GAD, SSRI or CBT should be proposed if functional impairment is marked. Two algorithms to guide GPs for the management of MDD and or the management of GAD...
Introduction
Antidepressants are widely prescribed in North America [1-3], in Europe [4], and above all in France [5,6]. General practitioners (GPs) are the main prescribers in North America [7] and in European countries [8-10]. The main reason for antidepressants prescribing by GPs is for a major depressive disorder (MDD), followed by a generalized anxiety disorder (GAD) [6,11]. GPs are the first caregivers involved in the diagnosis and treatment of MDD [10,12,13].

were created based on the data synthesis of this review. A GPs expert group discussed and adapted the algorithms to match with GPs expectancies.

Limits > Few articles dealt specifically with primary care practice, and only one meta-analysis of clinical trial on antidepressants in primary care was found.

Conclusions > From the best evidence-based data, we created two algorithms to guide GPs for the management of MDD and or the management of GAD. These algorithms will be implemented through a website available for GPs consultation.

Résumé
Prise en charge d’un premier épisode dépressif caractérisé ou d’un trouble anxieux généralisé chez l’adulte en soins primaires : une métarevue systématique

Contexte > Les médecins généralistes (MG) sont les premiers prescripteurs d’antidépresseurs en Europe et en France. Ces derniers éprouvent des difficultés pour mettre en œuvre les recommandations existantes dans leur pratique quotidienne.

Objectif > L’objectif de cette étude était d’élaborer deux algorithmes pour guider le MG dans la prise en charge des patients présentant un premier épisode dépressif caractérisé (EDC) ou un trouble anxieux généralisé (TAG), en soins primaires.

Sources documentaires > Les bases PubMed, Cochrane, et ISI Web of Science ont été explorées, utilisant principalement les mots-clés suivants: depressive disorder, anxiety disorders, antidepressive agents or antidepressant. La recherche sur PubMed a été réalisée via les termes du Medical Subject Heading (MeSH). La littérature grise a été également considérée au travers l’analyse des références des articles, des guides et recommandations de bonne pratique.

 Sélection des études > Une métarevue systématique (« overview of review ») incluant des revues systématiques, méta-analyses et guides et recommandations de bonne pratique, publiées entre janvier 2002 et décembre 2015, a été réalisée. Les grilles AGREE II, PRISMA et R-AMSTAR ont été utilisées pour évaluer la qualité méthodologique des études. Chaque étape a été réalisée indépendamment par deux chercheurs, selon les recommandations PRISMA. Une synthèse narrative portant sur les principales données cliniques à recueillir avant une prescription d’antidépresseurs en soins primaires, les informations à fournir au patient et le suivi recommandé, a été réalisée.

Résultats > Trente articles ont été inclus : 11 méta-analyses et 19 guides. Pour un EDC modéré à sévère, les inhibiteurs sélectifs de recapture de la sérotonine (ISRS) devraient être associés à une psychothérapie (thérapie cognitivo-comportementale (TCC)). Pour le TAG, les ISRS ou la TCC devraient être proposées si l’impact fonctionnel est marqué. Deux algorithmes destinés à guider les MG dans la prise en charge de l’EDC et du TAG ont été créés à partir de la synthèse des données de cette revue. Un groupe d’expert en MG a discuté et adapté les algorithmes pour correspondre au mieux aux attentes des MG.

Limites > Peu d’articles traitaient spécifiquement des soins primaires, et une seule méta-analyse, basée uniquement sur des essais cliniques en soins primaires, a été retrouvée.

Conclusions > Deux algorithmes élaborés à partir des données les mieux évaluées de la littérature ont été créés pour aider le MG dans la prise en charge d’un EDC ou d’un TAG. Ces algorithmes seront implémentés via un site internet disponible en consultation.
GPs face several challenges when dealing with depressive disorders, including diagnosis difficulties [14-16], and therapeutic difficulties, which were highlighted in Canada [17], in France [6,18-20] and in some other European countries, with compliance difficulties for the available recommendations [21]. Among French GPs, some are not aware of the MDD recommendations [22] and those who are, generally consider them little helpful in common practice [23]. Several factors limit physicians in implementing guidelines [24,25]. If recommendations usefulness is acknowledged, the need to improve them to better match GPs practice has been emphasized [26].

Improvement of clinical outcomes were shown when the guidelines were taken into account by physicians [25], particularly in mental health care [27,28]. Thus, focusing on guidelines implementation in daily practice may improve their use by physicians [29].

Besides, specific tools appropriate for primary care consultations are required, in particular, practical algorithms to apply during consultations and tips for prescriptions in order to better guide GPs first prescription of antidepressants [23,30]. For the moment, no such tool exists in French speaking countries. The implementation of these types of algorithms could be realized via an online tool as more and more GPs use internet during their daily practice [31-37]. Websites aiming to assist GPs in their practice are increasingly used in French speaking countries [38,39]. Some of them have been officially labeled [40]. A website aiming to guide GPs to deal with mental health care, derived from best primary care evidence-based studies, should improve practices and antidepressants prescription patterns in French speaking countries, as it was shown in the United Kingdom [28].

The objective of this study was to create two different algorithms to guide GPs for the management (diagnosis, treatments, follow-up) of adult patients presenting a first MDD (excluding bipolar disease) or a GAD episode, through a synthesis of guidelines, systematic reviews and meta-analyses. These evidence-based algorithms are created to be implemented through a website designed by a group of experts of teaching GPs.

Methods

We performed a systematic meta-review (overview) as described in the Cochrane handbook [41]. Currently, an increasing number of overviews is being published [42]. They make a synthesis of knowledge suitable for clinical practice [43]. Currently, an increasing number of overviews is being published [42]. They make a synthesis of knowledge suitable for clinical practice [43]. Currently, an increasing number of overviews is being published [42]. They make a synthesis of knowledge suitable for clinical practice [43]. Currently, an increasing number of overviews is being published [42]. They make a synthesis of knowledge suitable for clinical practice [43].

To be included, articles had to focus on adult patients in primary care, treated by antidepressants and potential associated drugs prescribed for a first MDD (excluding bipolar onset) or a GAD episode, with any complementary health care in parallel of these prescriptions. Articles included were published in English or French.

PubMed, Cochrane and ISI Web of Science were independently explored by two researchers in March 2015. Research equations used on these three databases are detailed below:


On Web of Science: TS = (Antidepress*) AND TS = (depress* OR anxiety) AND TS = (prescription* OR meta-analysis OR systematic review OR guideline*) AND Language = (English OR French).


On The Cochrane Library: Antidepressive agents. Limits: from 2002 to 2015, In Cochrane Reviews and Other Reviews. To ensure the currency of the data, this review was restricted to the twelve prior years (2002-2014). Grey literature was investigated on learned society websites, national and international health or medicine agencies, the National Guideline Clearinghouse website, and the Guideline International Network Website (GIN) identified by the Canadian Agency for Drugs and Technologies in Health Guide [48]. Keywords used were: antidepress*, antidepressive agent, depressive disorder, depre*, generalized anxiety disorder and anxiety. The references of included articles were also analyzed.

The study selection was performed through a two-step process: first, titles and abstracts of identified articles were screened, followed by reading the full-texts and articles fulfilling the inclusion criteria. Inclusion results were then pooled and discussed. For each selected article, method and quality of reporting were appraised in order to better control the quality of the meta-review [42,49-51]. Guidelines were evaluated by the AGREE II (Appraisal of Guidelines for Research and Evaluation) methodological rigor and transparency evaluation grid [52]. For meta-analyses and systematic reviews, the quality of reporting was assessed by the PRISMA checklist [53], and the methodological quality was assessed by the R-AMSTAR grid (Revised Assessment of Multiple Systematic Reviews) [54]. Studies were grouped according to the type of articles and classified by increasing rating. In addition, each researcher extracted independently relevant clinical data of each article within a pre-established synthesis grid built with the following items:
• indication and contraindication of antidepressants;
• situations where inpatient management is recommended;
• indication of drug;
• practical conditions for prescription;
• non-pharmacological care;
• investigation of clinical data and comorbidities before prescribing;
• information to provide;
• follow-up;
• specific contexts (elder people, pregnant women…).

A narrative synthesis was performed according to Popay et al. [55]: the two practical algorithms were created with the most relevant and best-evidence data extracted in the synthesis grids. Every data of these grids was included, unless a data was contradicted by a best-evaluated article or, in case of equality, by the most recent data. A GPs expert group, from the academic department of family medicine of Toulouse (including DD, JB, JD, MB, SO), discussed and adapted the algorithms issued from this synthesis, their design and their form, to match with GPs expectancies. Secondarily, a group of experts in psychiatry were asked to arbitrate non-consensual points. The result of this synthesis process is presented in two practical guides built for online algorithms. An update of the meta-review is planned every five years to implement new evidences in the website algorithms, as recentness is part of meta-reviews relevance [51].

Results

The article selection procedure (with reasons for exclusion) with a total of 21 articles is presented in figure 1. A list of excluded articles with detailed reasons for their exclusion is provided in supplementary material on the editor’s website. Ten articles were identified following grey literature exploration. Table I shows the characteristics of the articles focusing on MDD, while Table II deals with GAD. Each table is divided in two parts: one for the guidelines (n = 19), the other for meta-analyses (n = 11). Within each part, articles were prioritized according to their assessment score (best articles are at the top). Best articles assessment for depression was 84% for guidelines [56] and 93% for meta-analyses. For GAD, best assessment was 74% for guidelines [57], and above 82% for meta-analyses [58].

Two articles are dealing with both disorders and were integrated in each table. Detailed tables with method and quality assessment for each article are provided as supplementary material on the editor’s website.

Results on depression

Most of the studies used the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision) [59] or the ICD-10 (International Statistical Classification of Disease and Related Health Problems, 10th Revision) [60] for MDD diagnosis. Best-evidence studies agree on the greatest benefit of selective serotonin reuptake inhibitor (SSRI), and to a lesser extent, for serotonin norepinephrine reuptake inhibitors (SNSS), with no preference for any drug among each class [56,61,62]. Escitalopram and sertraline may have the best profile efficacy and acceptability [63]. These are also considered as the best cost-effectiveness drugs [63,64]. Due to their numerous adverse drug reactions, tricyclic antidepressants are considered as second intention drug. According to most guidelines [56,65–69], the treatment should be continued around 6 months after depression remission.

Adverse drug reactions can be a factor of non-adherence or discontinuation of treatment. Guidelines agree on the necessity to inform patients on adverse drug reactions (such as digestive troubles, headaches for SSRI and SNSS, or hypertension for SSNI), insisting on their mildness and transientness. Patients should be warned of the increased risk of anxiety, agitation and suicidal ideations at the beginning of the treatment, especially among those under 30 [56]. Physicians should insist on how to seek help in such situations. Most guidelines particularly insist on sexual dysfunction research, which is even more disabling in such psychiatric conditions.

The role of psychotherapy was discussed in most guidelines and specific meta-analyses of good evidence [70–72]. Even if we did not include specifically psychotherapy keywords in the research equations, several good evidence meta-analyses and guidelines dealt with the benefit of the association between pharmacotherapy and psychotherapy. The best-evidence meta-analysis [70] comparing pharmacotherapy to psychotherapy (PRISMA: 89%; RAMSTAR: 75%) preferred an association of these two therapies for moderate to severe MDD; whereas the best-evidence guidelines [56] preferred psycho- or pharmacotherapy for the same diagnosis severity (moderate to severe), with best-evidence for cognitive behavioral therapy (CBT). All guidelines underlined the limited place of benzodiazepines in primary care management of major depressive disorder: they should be only kept for acute anxiety, agitation and insomnia, for a short duration (2 weeks), and always in association, at antidepressant initiation. Guidelines enabled us to synthetize clinical key elements to collect before prescribing, information to provide and follow-up to schedule. They are detailed in the MDD management guide realized (figure 2). Before prescribing, hospitalization criteria should first be searched (suicidal crisis, isolation...), followed by psychiatrist follow-up criteria. Besides, lifestyle, history of addictions or organic diseases and drugs possibly prone to depression should be explored and should condition the management of the diagnostic approach and treatment choice. Identifying false beliefs about antidepressants (such as addiction), patient’s fears about his disease, and potential stigmatizations or discriminations linked to patient’s condition is recurrent in most good evidence articles [56,65], and would improve treatment adherence and the patient-physician confidence relationship.
Guidelines synthesis enabled us to determine specific populations prescription patterns (depending on age, organic comorbidities, specific features of depression). Information to provide to patients was also stressed: informing about the efficiency delay of antidepressants, the main and transient adverse drug reactions, the need to continue at least 6 months the treatment after remission, and the risk of relapse in the case of discontinuation, should contribute to the improvement of treatment adherence and prevent relapses. Finally, data compiled on the follow-up may help GPs to draw a schedule with their patients.

Results on generalized anxiety disorder
The definition of the DSM-IV-TR [59] was mostly used for GAD. The choice of antidepressants was divergent between studies. The best-evidence guideline advocates for the use of most SSRIs with the exception of paroxetine due to the withdrawal syndrome and toxicity risks in case of overdose [57]. Venlafaxine use was also recommended in second intention based on the toxicity risks arguments. The best-evidence meta-analysis advocates for tricyclic antidepressant, and also paroxetine and venlafaxine [58]. Data from the best-evidence guideline [57] was kept due to its recentness, and the recommendation of
<table>
<thead>
<tr>
<th>Evaluation Context</th>
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<th>Country</th>
<th>Article</th>
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<tbody>
<tr>
<td>Clinical guidelines</td>
<td>MDD without organic chronic disease. Mild MDD: avoid AD. Active monitoring 14 days. If persistence, or moderate to severe MDD: SSRI or CBT/interpersonal therapy/couples therapy. SSRI best benefit/risk ratio: no superiority between them. Treatment duration: at least 6 months after remission. See 1 week after if suicidal risk or below 30 years-old</td>
<td>18 years-old or more</td>
<td>Systematic review and recommendations elaborate by a development group</td>
<td>NA</td>
<td>NA</td>
<td>UK</td>
<td>NICE, Clinical Excellence, The British Psychological Society and The Royal College of Psychiatrists-2009 [56]</td>
</tr>
<tr>
<td>5% (AGREE II)</td>
<td>MDD: acute and continuation treatment phases. Treatment resistance. Dysthymia</td>
<td>Mild MDD: SSRI, NSRI (1st intention), imipraminic (2nd intention), Moderate MDD: SSRI, Severe MDD: SSRI, NSRI, imipraminic,</td>
<td>Adults, children, adolescents, pregnancy and breastfeeding</td>
<td>Systematic review, guide realized by expert group</td>
<td>NA</td>
<td>Yes</td>
<td>International Collaboration</td>
</tr>
<tr>
<td>65% (AGREE II)</td>
<td>New management of a MDD episode in primary care</td>
<td>Mild MDD: no AD in 1st intention Moderate to severe MDD: association psychotherapy and AD</td>
<td>18 years-old or more primary care patients</td>
<td>Review and consensus multidisciplinary group. Reading by external multidisciplinary group</td>
<td>Public</td>
<td>Yes</td>
<td>USA</td>
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<tr>
<td>63% (AGREE II)</td>
<td>Mild to severe MDD</td>
<td>MDD mild: non-pharmacological treatment in first intention. MDD moderate to severe: AD and psychotherapy eventually. SSRI in 1st intention. Elder people: SSRI</td>
<td>Adults but not pregnant women, in secondary or primary care</td>
<td>Development group and reading group</td>
<td>Public</td>
<td>No</td>
<td>Malaysia</td>
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<td>58% (AGREE II)</td>
<td>MDD</td>
<td>SSRI, NSRI and latest drugs in 1st intention, no difference between them. Between SSRI prefer escitalopram and sertraline. Imipraminics in 2nd intention (lower acceptability). Escitalopram superior to paroxetine or fluoxetine if severe depression. Avoid AD with children, or rather fluoxetine or citalopram</td>
<td>NA</td>
<td>Systematic review</td>
<td>Public</td>
<td>Yes</td>
<td>Canada</td>
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<td>55% (AGREE II)</td>
<td>Isolated MDD</td>
<td>SSRI or NSRI in 1st intention, imipraminic in 2nd intention for moderate to severe MDD, and</td>
<td>Adult in primary care, without</td>
<td>Review, multidisciplinary</td>
<td>Public</td>
<td>NA</td>
<td>France</td>
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<tr>
<td>Evaluation</td>
<td>Context</td>
<td>Main results</td>
<td>Population</td>
<td>Method</td>
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<td>Clinical guidelines</td>
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<td>53% (AGREE II)</td>
<td>MDD: acute and continuation treatment phases. Treatment resistance.</td>
<td>Mild à moderate MDD: pharmacotherapy (venlafaxine, escitalopram) OR psychotherapy Severe MDD: pharmacotherapy + psychotherapy</td>
<td>Adult, pregnancy, breastfeeding</td>
<td>Systematic review, expert group for guideline elaboration</td>
<td>NA</td>
<td>NA</td>
<td>UK</td>
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<td>52% (AGREE II)</td>
<td>Depressive disorder</td>
<td>1st intention: ISSRI, NSRI, other. Association to CBT, interpersonal therapy. Melancholia: imipraminics, NSRI, mirtazapine superior to SSRI Treatment duration: 1 years at least after first symptoms</td>
<td>Adults</td>
<td>Review then guidelines elaborate by multidisciplinary international group</td>
<td>NA</td>
<td>Yes</td>
<td>Australia</td>
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<tr>
<td>52% (AGREE II)</td>
<td>Depression and anxiety disorders</td>
<td>Mild MDD: AD equal to placebo. AD or psychotherapy, or both if bad adherence Moderate to severe MDD: SSRI, or NSRI, or other AD, in 1st intention, imipraminics in 2nd intention because of acceptability profile</td>
<td>Adults in primary or secondary care</td>
<td>Systematic review and recommendations elaborated by development group</td>
<td>Public</td>
<td>NA</td>
<td>France</td>
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<tr>
<td>45% (AGREE II)</td>
<td>MDD</td>
<td>Moderate to severe MDD: AD recommended. Psychotherapy recommended in acute phase of a mild to moderate MDD (CBT or interpersonal therapy).</td>
<td>Adult in primary care, without organic comorbidity, or pregnancy</td>
<td>Systematic review, multidisciplinary expert group and external reading group</td>
<td>Public</td>
<td>NA</td>
<td>Canada</td>
</tr>
<tr>
<td>43% (AGREE II)</td>
<td>Unipolar depression: acute phase, relapse, dysthymia</td>
<td>Mild MDD: no treatment psychotherapy; moderate MDD: psychotherapy and/or AD; severe MDD: psychotherapy and AD</td>
<td>18 years-old or more</td>
<td>Systematic review, consensus group</td>
<td>NA</td>
<td>Yes</td>
<td>Germany</td>
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<td>42% (AGREE II)</td>
<td>Depression</td>
<td>Mild MDD: lifestyle, close follow-up. Moderate MDD: imipraminics, or SSRI, or psychotherapy (CBT or interpersonal therapy) MDD severe: imipraminics or SSRI or venlafaxine or psychotherapy Treatment duration: 1 year at least</td>
<td>Patients in primary care</td>
<td>Systematic review, meta-analysis, guideline elaborated by a working group</td>
<td>Public</td>
<td>Yes</td>
<td>NZ</td>
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</table>

| Meta-analyses | | | | | | | | | 
| 96% (PRISMA) | Unipolar depression | Imipraminic and SSRI are more effective than placebo to treat MDD | Adults from 18 to 65, without comorbidities, in primary care | Systematic review then meta-analysis of randomised | Public | Yes | NZ, Australia, UK | Arroll-2009 [61] |
### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Meta-analyses</th>
<th>MDD</th>
<th>Adults</th>
<th>Systematic review and meta-analysis of 117 randomised controlled trials</th>
<th>No</th>
<th>Yes</th>
<th>UK</th>
<th>Cipriani A.–2009 [63]</th>
</tr>
</thead>
<tbody>
<tr>
<td>93% (PRISMA)</td>
<td>93% (R-AMSTAR)</td>
<td>MDD</td>
<td>Most effective AD are not the best tolerated: Sertraline and escitalopram have the best benefit/risk ratio</td>
<td>Adults</td>
<td>Systematic review and meta-analysis of 117 randomised controlled trials</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>89% (PRISMA)</td>
<td>75% (R-AMSTAR)</td>
<td>MDD</td>
<td>Psychotherapy and pharmacotherapy association is significantly superior to pharmacotherapy alone to obtain remission and prevent relapse in moderate to severe MDD</td>
<td>Subjects without neuro-psychiatric comorbidity, out of postpartum</td>
<td>Systematic review and meta-analysis</td>
<td>Public</td>
<td>No</td>
</tr>
<tr>
<td>78% (PRISMA)</td>
<td>64% (R-AMSTAR)</td>
<td>MDD from mild to severe, or chronic</td>
<td>AD associated with psychotherapy significantly superior to psychotherapy alone in moderate or chronic MDD</td>
<td>Adults</td>
<td>Systematic review and meta-analysis of 7 articles</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>78% (PRISMA)</td>
<td>61% (R-AMSTAR)</td>
<td>MDD</td>
<td>Escitalopram more effective to obtain remission, cost cost-effectiveness ratio.</td>
<td>NA</td>
<td>Meta-analysis comparing 10 antidepressive agents</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>74% (PRISMA)</td>
<td>66% (R-AMSTAR)</td>
<td>Depression and anxiety disorders</td>
<td>Psychotherapy more effective than imipraminics Other drugs were not more effective than psychotherapy</td>
<td>Adults</td>
<td>Systematic review and meta-analysis of 67 randomised controlled trials</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>70% (PRISMA)</td>
<td>64% (R-AMSTAR)</td>
<td>MDD</td>
<td>Pharmacotherapy is equivalent to psychotherapy</td>
<td>Adults</td>
<td>Systematic review and meta-analysis of 1237 articles</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>67% (PRISMA)</td>
<td>57% (R-AMSTAR)</td>
<td>MDD</td>
<td>Imipraminics are more effective than latest AD (SSRI, NSRI, others) when reviewing placebo-controlled trials (result probably linked to the evolution of clinical trials design through the last decades) Peadiatrics or elder populations excluded, neuro-psychiatric comorbidities excluded</td>
<td>Meta-analysis, Review over 30 years including placebo-controlled trials</td>
<td>Private</td>
<td>No</td>
<td>USA, Spain</td>
</tr>
<tr>
<td>48% (PRISMA)</td>
<td>58% (R-AMSTAR)</td>
<td>MDD, atypical depression</td>
<td>Mild MDD: monitoring time. If treatment: SSRI, venlafaxine, imipraminics (adverse drug reactions)</td>
<td>Adults, pregnancy, breastfeeding</td>
<td>Systematic review of meta-analysis</td>
<td>NA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AD: antidepressant; CBT: cognitive behavioral therapy; COI: conflict of interest; MDD: major depressive disorder; NSRI: noradrenaline, serotonin reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; NA: not available; NZ: New Zealand; UK: United Kingdom; USA: United States of America.

1Articles from grey literature review.

2Articles dealing both with anxiety and depressive disorders.
<table>
<thead>
<tr>
<th>Evaluation</th>
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<th>Article</th>
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<tbody>
<tr>
<td>74% (AGREE II)</td>
<td>GAD and panic troubles with or without agoraphobia</td>
<td>Mild/suspected GAD: no AD, close monitoring No improvement: low intensity psychotherapy No response, GAD with marked functional impairment: pharmacotherapy or psychotherapy of high intensity</td>
<td>Adults (18 or more) in primary or secondary care</td>
<td>Systematic review and recommendations elaborate by a development group</td>
<td>Public</td>
<td>Yes</td>
<td>UK</td>
<td>NICE, Clinical Excellence, The British Psychological Society and The Royal College of Psychiatrists-2011 [57]</td>
</tr>
<tr>
<td>66% (AGREE II)</td>
<td>GAD</td>
<td>SSRI: escitalopram, paroxetine, sertraline IRSN: venlafaxine eventually imipraminic OR psychotherapy (CBT)</td>
<td>Adults</td>
<td>Review by expert group</td>
<td>NA</td>
<td>NA</td>
<td>UK</td>
<td>Baldwin D.-2005 [74]</td>
</tr>
<tr>
<td>56% (AGREE II)</td>
<td>GAD, obsessive compulsive disorder, or post traumatic stress disorder</td>
<td>SSRI: escitalopram, paroxétine, sertraline NSRI: venlafaxine, duloxétine Imipraminics Psychotherapy: CBT</td>
<td>Adults</td>
<td>Expert consensus group</td>
<td>Private</td>
<td>NA</td>
<td>USA</td>
<td>Bandelow B.-2008 [73]</td>
</tr>
<tr>
<td>53% (AGREE II)</td>
<td>GAD, obsessive compulsive disorder, or post traumatic stress disorder</td>
<td>SSRI: escitalopram, paroxétine, sertraline NSRI: venlafaxine Psychotherapy</td>
<td>Adults</td>
<td>Comitee of 30 international experts: recommendations from randomised control trials</td>
<td>Private</td>
<td>NA</td>
<td>USA</td>
<td>Bandelow B.-2012 [87]</td>
</tr>
<tr>
<td>52% (AGREE II)</td>
<td>Depression and anxiety disorders</td>
<td>Lifestyle advices in 1st intention If pharmacotherapy: AD in 1st intention: venlafaxine, paroxetine, escitalopram, sertraline Duration: 6 month at least</td>
<td>Adults (18 or more) in primary or secondary care</td>
<td>Systematic review and recommendations elaborated by a development group.</td>
<td>Public</td>
<td>NA</td>
<td>France</td>
<td>Agence Française de Sécurité Sanitaire des Produits de Santé (AFFSAPS)-2006 [81]</td>
</tr>
<tr>
<td>40% (AGREE II)</td>
<td>Anxiety disorder</td>
<td>First intetion: SSRI and IRSN - paroxetine, escitalopram, venlafaxine - duration: 6 month at least Effectiveness equal to CBT Anxiolytics: benzodiazepine if rapid control of anxiety essential. Twelve weeks maximum, progressive withdrawal to limit anxiety rebound, withdrawal syndrom and addiction. Carefull if history of substance abuse or addiction</td>
<td>Adults (from 18 to 65)</td>
<td>Guide elaborated by a multidisciplinary team</td>
<td>NA</td>
<td>NA</td>
<td>France</td>
<td>Haute Autorité de Santé (HAS)-2007 [75]</td>
</tr>
</tbody>
</table>
### Table II (continued)

<table>
<thead>
<tr>
<th>Evaluation Context</th>
<th>Main results</th>
<th>Population</th>
<th>Method</th>
<th>Fundings</th>
<th>COI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical guidelines</strong></td>
<td>20% (AGREE II)</td>
<td>GAD according to DSM-IV criteria</td>
<td>Prefere venlafaxine, paroxetine</td>
<td>Treatment duration 2-28 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Meta-analyses</strong></td>
<td>89% (PRISMA)</td>
<td>Trouble anxieux généraux</td>
<td>Adults: prefer imipramine, paroxetine, venlafaxine.</td>
<td>Adults Randomised controlled trials review and meta-analysis</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>82% (R-AMSTAR)</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression and anxiety disorders more effective than psychotherapy.</td>
<td></td>
<td>Systematic review and meta-analysis of 67 randomised clinical trials</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults more effective than CBT.</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD: antidepressants and CBT: cognitive behavioral therapy.</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

**AD**: antidepressant; **CBT**: cognitive behavioral therapy; **COI**: conflicts of interest; **GAD**: generalized anxiety disorder; **NA**: not available; **NSRI**: noradrenaline, serotonin reuptake inhibitors; **SSRI**: selective serotonin reuptake inhibitors; **UK**: United Kingdom; **USA**: United States of America.

1. Articles from grey literature review.
2. Articles dealing both with anxiety and depressive disorders.


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sertraline in first intention, is not controversial in any other study. Besides, reasons to avoid venlafaxine and paroxetine prescription due to the risk of withdrawal syndrome or toxicity seems to be relevant in primary care practice, and results from the best meta-analysis are based on effectiveness only [58].

Most good-evidence guidelines recommend a treatment duration of at least 12 months [57,73,74]. Guidelines consider benzodiazepines use as controversial and advocate for short duration use at the beginning of an antidepressant treatment, in the acute phase [57,75,76].

FIGURE 2
Algorithm for the management of major depressive disorder in primary care

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Most good-evidence guidelines recommend a treatment duration of at least 12 months [57,73,74]. Guidelines consider benzodiazepines use as controversial and advocate for short duration use at the beginning of an antidepressant treatment, in the acute phase [57,75,76].
Psychotherapy can be an alternative to pharmacotherapy: its effectiveness is equivalent for CBT [57,72,75]. The patient preference and motivation for treatment should thus be discussed. Guidelines enabled us to synthesize the most important clinical data to look for before treating, the information to provide, and follow-up to schedule. These detailed data are provided in the GAD management guide realized (figure 3). Before prescribing, psychiatric data such as suicidal ideas, isolation, addiction, or other psychiatric condition, should be explored to determine whether a hospitalization or the transfer to a psychiatrist is necessary. In the same way as for the depression, identifying false beliefs about antidepressants, patient’s fears about its disease, and information to provide to the patient about his treatment and his condition, should contribute to the improvement of treatment adherence. Schedule the follow-up with patients also essential to improve treatment adherence and disease outcome.

**Discussion**

This is the first meta-review characterizing the main features of primary care management of diseases leading to antidepressants prescription, to implement decision algorithms through a website designed to be used during GPs consultations. According to the review performed, the best prescription pattern is the association of SSRI (or SSNRI in second intention) with CBT for severe to moderate MDD in primary care. The comparable effectiveness of antidepressant and CBT in GAD management for most impairing troubles was highlighted. This meta-review also highlights all the consultation tips and skills before and after prescription, including patient information.
Most articles based their disease definition on the DSM-IV-TR [59] since the studies and trials they included were set up before the DSM-5 publication [77]. In the DSM-5, for MDD diagnosis, bereavement is not an exclusion criterion anymore [78]. No substantial changes have occurred for GAD criteria [78]. According to the psychiatry experts, DSM-5 should be used by GPs, since it should become the new standard. The planned evaluation of GPs' expectations and satisfaction before broadcasting this tool as a website should explore, in particular, their point of view on DSM-5 use.

Meta-reviews usually include useful articles to enhance GPs access to evidence-based medicine [79]. Besides, the meta-review's method is suited to make a synthesis aiming to support clinical practice [43–45].

Even if meta-reviews can be prone to several weaknesses, already underlined [42,49–51], we tried to avoid them by following the PRISMA statement for its proceeding: we appraised the quality of included studies, we described the narrative synthesis process, we explored several databases, and we planned an up-to-date process. Best-evidence articles included had a high rating, up to 93%.

Our meta-review was focused on primary care outpatients only. Most meta-analyses were conducted from clinical trials [63,64], and only one included specifically primary care clinical trials [61]. Nonetheless, data from these explicit primary care articles were prioritized in case of discrepancy. Guidelines provided distinct recommendations for either inpatients or outpatients, enabling primary care data distinction. British guidelines of the National Institute for Health and Care Excellence (NICE) [56,57] have the best-evidence in our study, and most of our algorithm is based on its primary care data. To illustrate that point, one difficulty was to decide was between the recommendation of the use of any SSRI, as advocated in the only primary care Cochrane meta-analysis on antidepressants [61], or the preference for escitalopram and sertraline, as suggested in Cipriani et al. meta-analysis [63]. Both were almost equally evaluated. We chose to prioritize primary care data from Arroll et al. Cochrane Review of primary care trials. It was also confirmed by the psychiatry experts that aroused the necessity to refer to studies realized in real clinical practice context. Besides, GPs should choose the most appropriate SSRI, depending on the adverse drug reaction profile adequacy with patient's co-prescription and medical history. For instance, escitalopram, which is advocated in Cipriani's meta-analyses, should not be proposed as a default first intention choice before the GP lead his clinical reflection on QT lengthening risk of his patient.

Potential for selection and publication biases was considered during the whole review process by exploring international literature. Besides, 32% of the selected articles were extracted from grey literature, limiting publication bias. The two algorithms were established after a narrative synthesis with a predefined method [55], built after a GPs expert group to match GPs expectancies. To limit interpretation and subjectivity biases, the algorithms designed by a GPs expert group were based on the systematic meta-review that provided the hierarchized content of the algorithms thanks to the quality assessment.

Based on the synthesis of this meta-review, we created a set of tools to accompany GPs during their consultation: one algorithm for the management of MDD and one for the management of GAD. These algorithms are designed to provide an answer to GPs' difficulties in dealing with these conditions [23,30]. They will be implemented in a global project of a psychotropic drug prescription support website in French, accessible to GPs during their consultation. These algorithms will be used as a basis of the website content and architecture. An expert group of GPs and psychiatrists will assess the beta-version of the website. Then, a sample of GPs will evaluate the website content, relevance and ergonomic for daily practice, before its larger broadcast. Besides, an intervention study will assess the impact of the implementation of the website on psychotropic drugs prescription patterns improvement.

Acknowledgement: we would like to thank Pr Laurent Schmitt from the psychiatry department of Toulouse University Hospital, and Dr Maurice Bensoussan, psychiatrist in ambulatory care, for their expertise in the psychiatric field. We would also like to thank Dr Maryse Lapeyre-Mestre from the pharmacology department of Toulouse University Hospital for her precious methodological advices during this work.

Role of the funding source: no funding was required for this study.

Disclosure of interest: the authors declare that they have no competing interest.

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Management of first depression or generalized anxiety disorder episode in adults in primary care: A systematic metareview

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To cite this article: Driot D, et al. Management of first depression or generalized anxiety disorder episode in adults in primary care: A systematic metareview. Presse Med. (2017), https://doi.org/10.1016/j.pmed.2017.10.010

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