

Discontinuation of Antidepressants in Older Adults: A Literature Review

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Abstract: Polypharmacy increases the risk of unbearable side effects, drug–drug interactions, and hospitalizations in geriatric patients. The iatrogenic risk of inadequate management of antidepressants is very important in this population. Therefore, primary care physicians and geriatricians have the responsibility of the optimization of antidepressants prescriptions. Our work is a literature review of the European and the international guidelines regarding the management of antidepressants. We reviewed the PubMed database and Google scholar for articles and reviews from 2015. We also screened relevant articles for more references and searched the web for available European guidelines relevant to our topic. We divided our findings into four main inquiries that are Indication, effectiveness, tolerability, and iatrogenic risks. Poor or absence of effectiveness should lead to a readjustment of the treatment plan. In case of unbearable side effects, antidepressants should be stopped, and alternative non-pharmacological therapies should be proposed. Doctors should look out for drug–drug interaction risks in this population and constantly adjust the prescription. Prescription of antidepressants is not always evidence based which leads to heavy iatrogenic consequences. We suggest a simple 4-questions-algorithm that aims to remind doctors of the basics of good practice and helps in the process of deprescribing an antidepressant in older adults.

Keywords: older adults, antidepressant, management, deprescribing antidepressant

Introduction

As older adults have medical prescriptions that are usually a source of iatrogenic risk,¹ both the Haute Autorité de Santé (HAS)² and the National Institute for Clinical Excellence (NICE)³ are pointing the fact that medical prescription should always be optimized. Indeed it has been over two decades since the HAS has been raising awareness of the risk of potentially inappropriate drugs (PID) in older adults and encouraging physicians to follow meticulously the recommendations of good practice.⁴ In the same context, the NICE has issued various guidelines regarding the assessment and management of polymorbidity in older people.⁵ In fact, up to 50% of patients over 60 years old are polymorbid⁶ this makes it mandatory to review the patient prescription to check for PID or newly prescribed non-indicated drugs in order to reduce polypharmacy.¹ While admission in a geriatric ward is an opportunity for stopping non-indicated drugs,^{5,7,8} antidepressants need to be handled extra-carefully because their abrupt discontinuation can result in severe withdrawal symptoms thus altering the clinical situation.⁹ A summary of discontinuation symptoms is presented in Table 1. These symptoms have been described by both the NICE and HAS.

Although antidepressant indications are practically the same in older adults as in the general population, the management is completely different in this particular population. Many other criteria should be considered before initiating or stopping such treatments like comorbidities, drug–drug interactions and severity of the depression. The European guidelines are clear regarding the role of primary care physicians and geriatricians in the management of polymorbidity and drug interaction risks. Doctors have the responsibility to stop inappropriate drugs when they exist in order to preserve the quality of life of their older patients.^{3,5,7}

Table 1 The Most Common Symptoms of Discontinuation of Antidepressants

Study	Pharmacologic Class	Potential Withdrawal Symptoms
(27)	SSRI	<ul style="list-style-type: none"> • Dizziness, lightheadedness, vertigo or feeling faint • Paresthesia • Anxiety • Diarrhea • Fatigue • Gait instability • Headache • Insomnia • Irritability • Nausea and/or emesis • Tremor • Visual disturbances
(50)	TCA	<ul style="list-style-type: none"> • Somatic symptoms: nausea, emesis, headache, fatigue • Sleeping disorders: insomnia, nightmares • Movement disorders: akathisia, Parkinsonian syndrome. • Behavioral activation: Mania, Hypomania, panic attacks. • Heart rhythm disorders
	MAOI	<ul style="list-style-type: none"> • Psychotic symptoms: delirium, hallucination, catatonia • Agitation and Aggressiveness • Behavioral activation: mania, hypomania

Abbreviations: SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant; MAOI, Monoamine Oxidase Inhibitor.

Looking into recent literature we found out that management of antidepressants in older adults¹⁰ as well as investigation of tolerability and effectiveness were explored by many authors^{11,12} in different papers but there were no literature reviews focusing on discontinuation of antidepressants in older adults from a geriatric point of view. To our best knowledge, this is the first paper to focus on the question of discontinuing antidepressants in older adults specifically.

Our aim is to review the international literature in order to establish a framework that could help general practitioners and geriatricians with the assessment and the decision-making process regarding whether deprescribing an antidepressant in older adults.

Methods

To find the related articles, the keywords alone in combination “depression”, “elderly”, “depressive disorders”, “adverse event”, “antidepressive treatment”, and “older adults” were searched in the Medline and Google Scholar databases. The inclusion criteria were English or French language, the publication date of the paper after 2017, randomized controlled trials reported as full-text. To determine the eligibility of the articles, those including one of the keywords in their titles or abstract were first selected.

This search identified 657 full articles and 10 meta-analyses. The titles and abstracts were examined for relevance to our subject. Other references were screened for in the relevant articles that we retained for our review.

We also consulted the official website of the Haute Autorité de Santé (HAS) (<https://www.has-sante.fr/>), the National Institute for Clinical Excellence (NICE) (<https://www.nice.org.uk>) and the Nationale Versorgungsleitlinie Depression (NVLD) (<https://www.awmf.org>) for guidelines regarding antidepressants management in geriatrics and polymorbidity.

Results

Through our research, we found that management of antidepressants in late life depression is not always evidence based.¹³ Effectiveness and tolerability of pharmacologic as well as non-pharmacologic therapies were tackled in many original articles and meta-analyses that we included in our literature review. These meta-analyses are presented in Table 2.^{11,12,14–18}

Table 2 Selection of Meta-Analyses of Primary Outcomes of Different Antidepressant Therapies in Older Age

Source	Nb of RCTs and Blindings	Age (Years)	Frailty	Nb of Patients	Primary Outcome
(14)	44 RCT	Over 65	NA	6373	The very first meta-analysis and systematic review to investigate the response rate of AD in adults older than 65 years old. Older patients with MDD did not show difference from the one in the general adult population regardless the pharmacologic class of the AD. 50.7% of patients showed at least 50% reduction of their HDRS baseline.
(15)	9 trials Double blinded	Over 65	Non-Frail	2704	Effectiveness of AD is low in older patients with no obvious characteristics of frailty. RR with second-generation AD 45.3% VS Placebo 40.5% (95% CI: 0.96–1.37; $p=0.12$) while adverse effects seem to be a motive of discontinuation, AD 13% vs Placebo 5.8% (95% CI: 1.45–363; $p < 0.001$).
(11)	53 RCT	Over 65	NA	9274	116 adverse effects were identified and analyzed in pairwise meta-analyses to help with the decision-making process in patients with MDD. The overall evidence for non-pharmacological treatments in MDD is insufficient due to poor available data. Only 5 out of the 53 RCTs provided usable data. (Neither network nor pairwise meta-analyses were possible).
(16)	19 RCT's and 2 observational studies	Over 65	Non-frail	NA	SNRIs are significantly more associated with side effects than placebos. SNRIs and SSRIs both increased withdrawals due to side effects during the acute phase of the MDD. The studies of this metanalyses excluded patients with multiple comorbidities and other neuropsychotic disorders which is not concordant with the reality of older people who have polypharmacy and polymorbidities.
(17)	10 RCTs and 1 Cohort Study	Over 60	NA	1529 RCT 14 Cohort	Individual CBT and bright-light therapy had promising results in primary care patients. Better quality research is needed to investigate other non-pharmacological therapies such as exercise, PST or Behavioral activation.
(18)	14	Over 65	Frail	NA	CBT, PST are psychological therapies that are showing promising results and seem to be a solid option for frail old patients but are to be further explored especially regarding generalizability, safety and cost effectiveness because of the few trials included in this meta-analysis
(12)	12	Over 65	NA	NA	Most of the participants in this meta-analysis did not reach remission after 8 weeks of treatment. The author recommends early detection of “non responders” in order to find effective treatment options for this group.

Abbreviations: RCT, Randomized Control Study; MDD, Major Depressive Disorder; HDRS, Hamilton Rating Scale for Depression; RR, Response Rate; CI, Confidence Interval; SNRIs, Serotonin-Norepinephrine Reuptake inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors; CBT, Cognitive and Behavioral Therapy; PST, Problem Solving Therapy.

In a metanalysis, of 44 Randomized Control Trials (RCTs) the authors evaluated the response rate (RR) of AD in older adults and found out that RR was the same as in younger adults.¹⁴ Even though effectiveness of AD treatments vs placebo in older patients did not show any difference from the general adult population.¹⁴ However, bad tolerability of the treatment and the risk of adverse effects in the aging population are the main cause to discontinue AD.¹⁵ In another large meta analyses of 53 RCTs, the authors identified 116 adverse effects of AD and their correlation to each molecule.¹¹ In general, studies have shown that the effectiveness and the tolerability of the AD in older adults depend on the pharmacologic class¹⁶ and that early detection of “non-responders” is mandatory in order to adapt the treatment plan.¹²

Non-pharmacologic therapies like Cognitive Behavioral Therapy (CBT) and other alternative therapies can be of help in case of a mild to moderate depression^{17,18} and especially in case of polymorbidity.

In order to assess the prescription of an AD in older adults, we suggest that physicians respond to four main questions in the following order of priority: relevance of indication, AD effectiveness, AD tolerance, and proper choice of AD treatment. After going through these four points, physicians can justify appropriately the discontinuation of an AD.

Relevance of the Indication of the AD Treatment

The international literature and the European guidelines clearly state that the indications for AD are the same for older adults.^{2,7,8,19,20} The prescription of AD for patients over 65 years old with comorbidities should only be offered in severe forms of depression.^{7,20} Otherwise, for mild to moderate depressive disorders physicians should start with psychotherapy.

Whenever an older adult is admitted in a hospital ward, physicians should check that the AD is still indicated. The absence of indication should alert the physician to consider reevaluating the treatment plan.^{2,4} Misuse of AD is directly related to the quality of the initial diagnosis which can be difficult with the advancing age.^{13,21,22} Older adults usually present with somatic symptoms or behavioral disturbances, masking the depression episode less obvious and leading to undiagnosed or incorrectly treated depression.²¹ In case of doubt, physicians should rely on valid diagnostic tools such as the Geriatric Depression Scale (GDS)²³ or the Patient Health Questionnaire 9 (PHQ 9)²⁴ to validate the diagnosis.² The Hamilton Rating Scale for Depression (HDRS)²⁵ could be used to re-evaluate the patient's state and assess the gravity of the actual episode.² For very old and frail patients who suffer from one or more conditions other than depression, the diagnosis and the level of severity must be confirmed with the collaboration of the geriatrician and the psychiatrist.

In case of absence of indication and when the AD has been recently prescribed (less than 4 weeks)²⁶ the treatment should be stopped gradually over a 4-week period without risking discontinuation syndrome but particular attention should be paid to AD with a short half-life (such as paroxetine and venlafaxine).^{8,20} Furthermore, physicians should keep in mind that the AD could be prescribed for other situations such as: neuropathic pain, anxiety disorder or panic disorder. However, if the AD has been prescribed for long period of time in the context of a documented clinical depression, physicians should review the situation depending on whether or not the patient is in remission.⁹ In a recent review, the author suggested a simple and helpful algorithm for the management of AD maintenance therapy in older adults. This algorithm states that if a patient has been diagnosed with a first episode of depression and achieved remission for 1-year treatment could be discontinued gradually, if this is the second episode of depression then the patient should continue treatment for one additional year. In case of third episode of depression, the treatment could be renewed for at least 2 years or even indefinitely.¹⁰ This approach was adopted by the HAS in order to establish guidelines regarding the management of antidepressants.²

In case of mild to moderate depression, the European guidelines recommend that first-line CBT and psychotherapy may also be sufficient as monotherapy.^{2,7,8,20} There is no scientific proof of superiority of one non-pharmacological therapy over another in treating depression in old age.^{2,17,18}

Patients under AD should be closely monitored and continuously reevaluated through screening for treatment resistance or unbearable side effects.^{10,27,28}

There are no evidence-based guidelines on the duration of treatment with antidepressants when prescribed in neuropathic pain, anxiety, or panic disorders in old age. In this case, there are no clear guidelines or literature regarding the therapy duration nor the indication of discontinuation.

AD Effectiveness

Antidepressants have been proved helpful in treatment of major depressive disorder and are significantly more effective than placebo.¹⁴ However, physicians should keep in mind that older adults have forms of depression that are naturally resistant to drugs, particularly, those with cerebrovascular damage²⁹ and anxious forms of depression.³⁰ About 50% of older patients do respond to antidepressants but they tend to take longer time to achieve clinical remission.¹⁴ These findings were already described in a literature review as the response rate to treatment was significantly higher in studies with a longer trial period (10–12 weeks).³¹ The latter suggests that the typical period of four to eight weeks may not be sufficient to see a response in older

adults.^{13,31,32} The effectiveness of antidepressants was measured by the clinical response after 12 weeks of treatment and most of the studies evaluated the response of antidepressants based on the reduction rate on the Hamilton Depression Scale (at least 50% from baseline).^{14,15}

In case of ineffectiveness, the treatment plan must be revised by increasing the initial AD dose, switching to another AD or augmenting the AD with other agents.^{2,33}

When switching an AD by another one, physicians should be careful and make sure they respect the guidelines to avoid both discontinuation syndrome and iatrogenic risk.² In a recent cohort, the authors studied the antidepressant switching patterns in older adults in long-term care facilities. Their results showed that almost half of the switches were not in line with the actual guidelines. They also noticed that some switch strategies were harmful and increased the iatrogenic risk among older adults.³⁴ There is no clear consensus about which AD should be switched to in case of ineffectiveness, patients can be switched to antidepressants from the same pharmacologic class or to a different one.³³ There are 3 possible switching strategies: immediate switching, cross tapering, or after incorporating a washout period depending on the AD pharmacologic class.³⁵ Immediate switching is generally possible when substituting a selective serotonin reuptake inhibitor (SSRI) or a serotonin and noradrenaline reuptake inhibitor (SNRI) for a drug from its own class, but this strategy requires clinical expertise as patients can develop symptoms of serotoninergic syndrome.^{35,36} For polymorbid patients, a 2 to 3 weeks washout period when switching to and from monoamine oxidase inhibitors (MAOI) is mandatory^{35,36} but for older age these antidepressants are not recommended. The most optimal strategy in old age would be the gradual tapering of the dose over 4 weeks before proceeding with a washout period of 5 half-lives of the drug.³⁵ The international literature highlights the risk of exacerbation of the depressive disorder in case of switching antidepressants, in addition to possible discontinuation symptoms.^{2,8,20,35}

Tolerance of the AD Treatment

The European guidelines affirm that older adults can be treated in the same way as younger patients, but the poor tolerability of antidepressants requires close monitoring, especially during treatment initiation.^{2,8,20} Nonetheless, the golden rule adopted by the international geriatric community states: “start low, go slow”.

For the older age, the NVLD suggests to start antidepressants with a low daily dose (preferably half the recommended dose for young adults).²⁰ As for the HAS and the NICE physicians should monitor closely the initiation of an AD and screen for symptoms or signs of bad tolerability.^{2,7,8}

Due to their important anticholinergic load, tricyclic antidepressants (TCA) should not be considered for older adults and must be discontinued if the patient presents with glaucoma, conduction heart disease, prostatism or delirium.³⁷ Furthermore, patients under TCA had a significantly increased risk of falling and subsequent fractures due to the effects of these drugs on coordination, motor activity and balance.³⁸ Also, in a recent large prospective study of 71,515 patients over 60 years old, the authors established a link between dementia and taking an AD.³⁹ In response to this study, the risk of having dementia was attributed to the anticholinergic activity of antidepressants.⁴⁰

Some patients tend to discontinue their AD by themselves due to decline in their quality of life (mainly due to gastro-intestinal symptoms and sedation).⁴¹ Side effects that seemed to be observed in adult population, such as metabolic syndrome or erectile dysfunction, were not described in older subjects.⁴⁰ The International guidelines point that particular attention should be paid to the risk of falling, fractures, hyponatremia, gastrointestinal bleeding (associated with SSRI) and prolongation of the QT interval on the EKG.^{2,7,8,11,16,20}

Psychotherapy, CBT, Transcranial Magnetic Stimulation (TMS) or Electroconvulsive Therapy (ECT) can be proposed as a monotherapy or associated with other drug therapies in case of bad tolerability. In this case, the patient should be addressed to a psychiatrist for specialized care.³³

Proper Choice of AD

Reviewing the prescription upon admission in a hospital ward is a fundamental step in the process of geriatric assessment.⁵ Physicians should screen for potentially inappropriate drugs (PID) in patients under antidepressants to prevent any drug–drug interactions. The European guidelines encourage physicians to pay attention to any association of medications that may increase the anticholinergic load.^{2,5,7}

SSRIs are favored by the international community as a first-line treatment for major depressive disorder, but special attention should be paid to risk of hyponatremia, diarrhea, agitation and gastrointestinal bleeding (especially when associated with non-steroidal anti-inflammatory drugs).^{2,7,8}

To detect PID, physicians can rely on different helpful tools. In 1991, the Beers' criteria were the first tool used to detect PID in older adults. This tool targets a list of drugs where their risk of harm outweighs their benefit.⁴² In 2008, was published a more reliable tool regarding management of medication in older age called: The Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START). This tool suggests not only, the discontinuation of PID but also those that should be initiated in older age.⁴³ Both the STOPP/START and Beers criteria are based on literature review and consensus validation among an international panel of experts.^{42,44}

The Beers criteria explicitly cites (amitriptyline, amoxapine, clomipramine, désipramine, doxépine, imipramine, nortriptyline, paroxétine, protriptyline, trimipramine) as potentially inappropriate drugs that require considering their discontinuation.⁴⁵ The

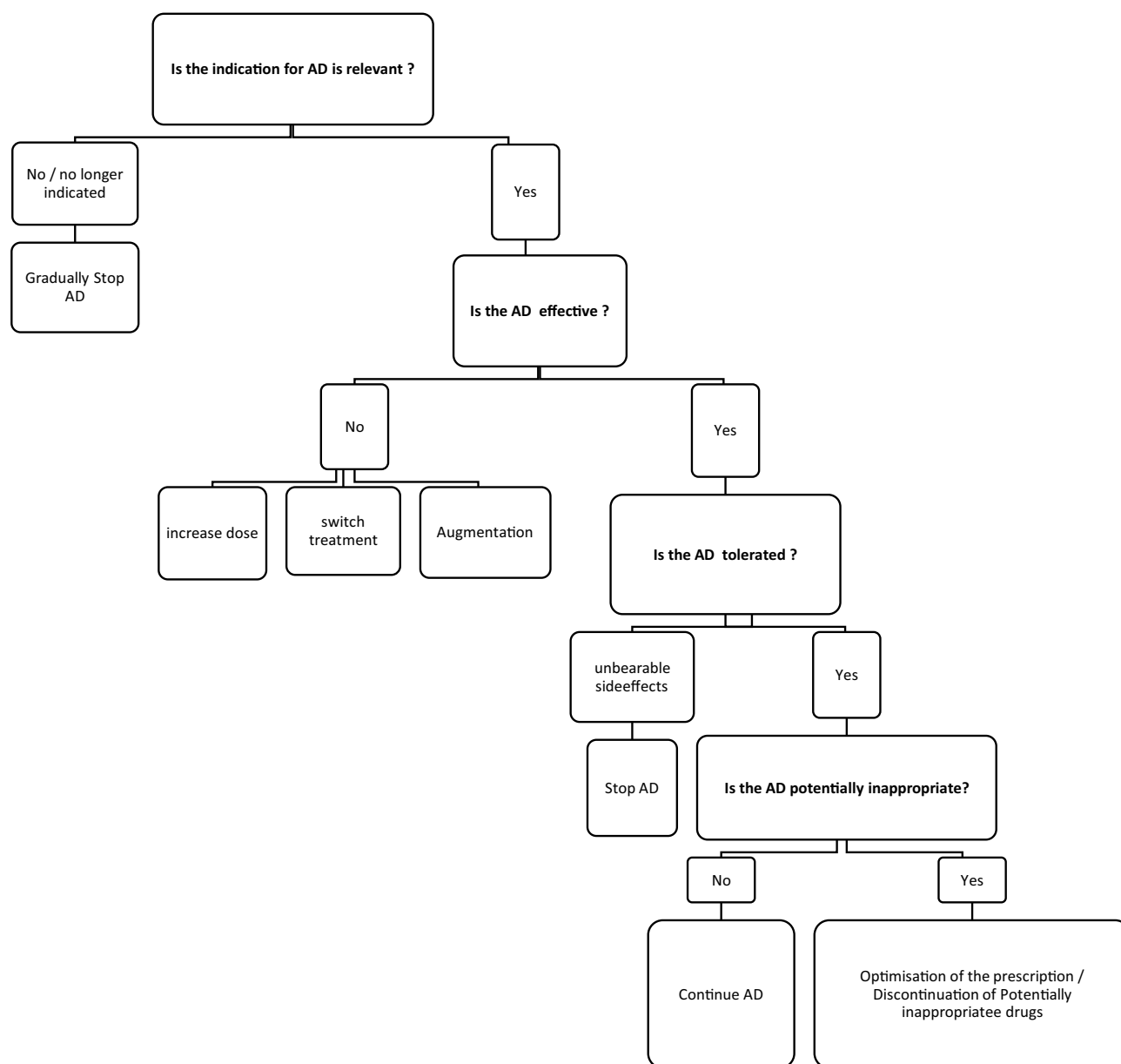


Figure 1 Suggested algorithm for management of antidepressant in older age.

STOPP/START does not include specific ADs in their STOPP part and only recommends discontinuing any treatment that have no clinical indications.⁴⁶ With these tools, screening for PID became evidence based and easily accessible to every practitioner.⁴⁰

The international bibliography seems to favor the STOPP/START over the Beers Criteria as a more adequate tool. In fact, a 2013 Australian study comparing Beers criteria versus STOPP/START concluded that the number and range of identified drug-related problems was best represented by STOPP/START criteria.⁴⁷ In 2011, a study highlighted that, unlike Beers, STOPP/START criteria have been shown to be significantly associated with avoidable adverse drug events that cause or contribute to urgent hospitalization.⁴⁸

Conclusion

Our review of the European and international literature concluded that AD management in older patients is not evidence-based. When no longer needed or in case of absence of indication, antidepressants should be discontinued gradually (Preferably over a 4-week period) to prevent discontinuation syndrome. The ineffectiveness of a first-line AD is not a cause for discontinuation but a motive to review the treatment plan and in case of resistance to seek psychiatrist expertise for specific therapies. Geriatric expertise is necessary to optimize the treatment plan and limit drug interaction risks by stopping potentially inappropriate drugs, the STOPP/START tool along with Beer's criteria is very helpful in this situation.

We suggest an algorithm based on four important steps that should be addressed rigorously before considering discontinuation of antidepressants in older adults (Figure 1).

Disclosure

The authors report no conflicts of interest in this work.

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