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REVIEW

Switching antidepressants

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Abstract

Switching antidepressants because of lack of efficacy or unacceptable side-effects, while often required in general practice, may result in toxic drug-drug interactions, worsening depression or unpleasant discontinuation reactions. Switching strategies to minimise these risks include immediate switching, cross-tapering or incorporating a washout period. Immediate switching is generally possible when substituting a selective serotonin reuptake inhibitor or a serotonin and noradrenaline reuptake inhibitor for a drug from its own class. Cross-tapering over a period of weeks is preferred when switching between different antidepressant classes or from high-dose antidepressants. Dangerous interactions necessitate the observance of an adequate washout period when switching to and from monoamine oxidase inhibitors.

Keywords: switching antidepressants, discontinuation reactions, immediate switching, cross-tapering, washout period

Introduction

Antidepressants are widely prescribed for depression in primary care,[1] but a lack of efficacy and/or intolerable side-effects often necessitates switching to an alternative antidepressant.[2] Although side-effects such as anxiety, headaches, nausea and insomnia generally wane with continued treatment, approximately 10% of patients require a change of medication for persistent adverse effects.[3] It is particularly challenging to know when and how to change the antidepressant drug treatment plan for the 40% of patients who fail to achieve an adequate response.[3]

Guidelines recommend assessing patient response after a four-week trial of an antidepressant taken at the full therapeutic dose. If there is at least some improvement, treatment should be continued with the same antidepressant for another 2-4 weeks. However, if there is no sign of continuous improvement, the next step in treatment should be considered because the likelihood of eventual response diminishes if there has been no response by this time.[4]

Next-step treatment should also be considered if there is only minimal improvement at the 6-8 week assessment, unless patients have failed a number of treatments, then longer trials may be considered. Patients should continue their initial antidepressant if there is evidence of moderate or greater improvement at this assessment point.[4]

Next-step treatment

There are several pharmacological approaches to patients who fail to respond sufficiently to antidepressant medication. These include increasing the dose (if there has been a partial response and the side-effects are minimal), switching to an alternative antidepressant (if there are troublesome or dose-limiting side-effects, and/or there has been no improvement), or augmenting the current drug with another (when there has been a partial or insufficient response on the current antidepressant, and switching antidepressants has been unsuccessful).[5] Of these, switching (which incidentally has a wide range of response rates from 12-70% in clinical trials) is often preferred in primary care. Initial switching is reasonable either within or between antidepressant classes, while a different antidepressant class is probably indicated after more than one failure within a specific class.[4]

Potential pitfalls in switching

Perilous drug toxicity due to pharmacodynamic or pharmacokinetic drug-drug interactions,[6] worsening depression[7] and discontinuation symptoms are the major concerns when switching from one antidepressant drug to another.[8,9]

A survey of 817 patients by the Royal College of Psychiatrists revealed that discontinuation reactions occurred in approximately 60% of people who stopped their antidepressants, and generally lasted six weeks, although a duration exceeding 12 weeks was not unusual. The most common symptom experienced by this self-selecting group of respondents was severe anxiety (70%), followed by moderate dizziness (61%), vivid dreams (51%), electric shocks (48%), stomach upsets (33%) and flu-like symptoms (32%). The less common symptoms of returning depression (7%), headaches (3%), suicidal thoughts (2%) and insomnia (2%) were considered severe by patients. Although all antidepressants are capable of causing discontinuation symptoms,[9] this survey showed that antidepressants with a high propensity for discontinuation symptoms include venlafaxine, duloxetine, paroxetine and escitalopram; those with a medium propensity, sertraline, citalopram and tricyclic antidepressants; and those with a low propensity, fluoxetine, agomelatine and mirtazapine.[10] The findings of this naturalistic study correlate with those from published clinical trials in which venlafaxine and

paroxetine were often associated with an increased propensity for causing discontinuation symptoms compared to other antidepressants,[9] but which differed markedly in the incidence of discontinuation symptoms (60% vs. 30%), possibly reflecting the self-selecting nature of the participants or under-reporting in the clinical trials.

Discontinuation reactions may occur when switching antidepressants, although theoretically not as common as when stopping antidepressants altogether, particularly when switching between antidepressants with different mechanisms of action, or when switching from drugs with short half-lives.[11] Discontinuation symptoms that follow antidepressant switching may be incorrectly ascribed to the side-effects of the new antidepressant, which may be stopped on the assumption that the patient is unable to tolerate it.[9] Furthermore, discontinuation reactions may be mistaken for worsening depression, leading clinicians to incorrectly conclude that the new treatment is ineffective. As a result, the antidepressant dose may be increased, or an augmentation strategy adopted unnecessarily.[9] Therefore, an appreciation of antidepressant pharmacology, as well as the ability to distinguish between discontinuation symptoms, toxic effects and worsening depression, is crucial when effecting the change. Rational antidepressant switching strategies aim to minimise these pitfalls.

Immediate switching

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed first-line antidepressants for major depressive disorder, with response rates of 50-60%. Switching within or between classes of antidepressants is often required in patients with an insufficient response to SSRIs.[12] Because they share a similar mechanism of action, the immediate substitution of one SSRI for another is probably the easiest switching option in general practice. Usually, the first SSRI is stopped abruptly, and the new SSRI initiated immediately at the former therapeutic equivalent dose (Table I), although considering the idiosyncratic nature of some adverse effects, an initial lower dose may be considered, when appropriate.[5] Discontinuation reactions and emergent or worsening depression are minimised by immediate switching. After more than one SSRI failure, a serotonin and noradrenaline reuptake inhibitor (SNRI), such as venlafaxine, should be considered as an alternative.[4]

Switching from a normal therapeutic dose of an SSRI to an equivalent dose of an SNRI may also be accomplished by immediate switching because of the overlap in pharmacology at these doses[5] (Table I). The exceptions are when switching from fluoxetine or paroxetine, because these SSRIs inhibit the metabolism of duloxetine and venlafaxine. Therefore, a lower initial dose of the SNRI is recommended to avoid toxic effects. It should be noted that fluoxetine may continue to inhibit cytochrome P (CYP) 2D6 metabolising enzymes for up to five weeks because of the long half-life of its active metabolite, norfluoxetine, and caution is needed for this extended period.[13]

Similarly, immediate switching of one SNRI to another is considered relatively simple, provided the doses are low. Substituting venlafaxine at doses below 150 mg for duloxetine at doses below 60 mg is generally well tolerated.(Table I) When switching at higher doses, a cross-taper is preferred in order to reduce the potential for drug toxicity.[5]

Table I: Antidepressant classes and doses[14]

Antidepressant	Usual starting dose (mg/day)*	Usual therapeutic dose (mg/day)*
Selective serotonin re-uptake inhibitors		
Citalopram	20	20-40**
Escitalopram	10	10-20
Fluoxetine	20	20-60
Fluvoxamine	50	50-200
Paroxetine	20	20-40
Sertraline	50	50-200
Serotonin and noradrenaline re-uptake inhibitors		
Desvenlafaxine	50	50
Duloxetine	30-60	30-120
Milnacipran	12.5	100-200
Venlafaxine	37.5-75.0	75-375
Venlafaxine XR	37.5	75-225
Atypical agents		
Agomelatine	25	25-50
Bupropion	200	300 (maximum single dose 150 mg)
Bupropion XL 24 hour	150	300
Mirtazapine	15	15-45
Tricyclic antidepressants		
Amitriptyline	25	150-300
Clomipramine	25	100-250
Desipramine	25	150-300
Imipramine	25	150-300
Nortriptyline	25	50-150
Monoamine oxidase inhibitors		
Isocarboxazid	10	10-40
Phenelzine	15	15-90
Tranylcypromine	10	30-60

* Consider a low dose when switching from one antidepressant to another, initiating an antidepressant, or maintaining an antidepressant, in elderly, medically compromised (e.g. renal or hepatic illness) or drug-sensitive patients, as well as patients with a low body mass index, or when switching from antidepressants that inhibit the CYP2D6 enzyme

**The maximum recommended dose of citalopram is 20 mg for patients > 60 years of age, with significant hepatic insufficiency, or those taking interacting medications which could increase citalopram levels

Cross-tapering

Cross-tapering involves reducing the dose of the initial drug gradually over a period of 1-2 weeks, while introducing and slowly increasing the dose of the subsequent antidepressant to a therapeutic equivalent dose over this time. The advantages of cross-tapering include minimising the risks of drug toxicity, discontinuation reactions and worsening depression. A longer (2-3 weeks) cross-tapering period is recommended when switching from an SNRI in order to circumvent venlafaxine's high propensity for causing uncomfortable discontinuation symptoms, and duloxetine's potential to cause drug toxicity

through its inhibition of the subsequent antidepressant metabolism.[14]

As a general rule, cross-tapering is recommended when switching between drug classes or when doses of the initial antidepressant are high, such as when switching from a high-dose SSRI to an SNRI, or from high-dose venlafaxine to duloxetine. Thus, switching from an SSRI to a tricyclic antidepressant (TCA); from an SNRI to an SSRI, or to any other antidepressant; and from or to TCAs, or mirtazapine, agomelatine, reboxetine or bupropion, typically involve cross-tapering.

When switching, it should be noted that most SSRIs, as well as bupropion, inhibit CYP2D6 enzymes to some degree.[15] This may result in higher plasma levels of co-administered antidepressants that utilise this pathway for their metabolism. Although most SSRIs are cleared from the body within five days, fluoxetine requires five weeks for complete elimination.

Therefore, when cross-tapering from an SSRI (particularly fluoxetine, paroxetine and fluvoxamine, which have a high potential for inhibiting TCA metabolism), the TCA should be started at a very low dose owing to the risks of potentially fatal cardiotoxicity. Where the switch is from fluoxetine, the TCA should be prescribed at this reduced dose for a period of five weeks to avoid this hazardous drug-drug interaction. If in doubt, TCA blood levels should be monitored during this period.

Similarly, because of enzyme inhibition, the co-prescribing of higher doses of bupropion with fluoxetine, paroxetine or fluvoxamine during the cross-tapering process could cause bupropion-induced seizures.[16] For this reason, lower-than-normal doses of bupropion are advised when cross-tapering.

Washout period

Dangerous drug interactions and severe toxicity, such as serotonin syndrome[17] and hypertensive crisis, are associated with the concomitant administration of monoamine oxidase inhibitors (MAOIs) and other antidepressants.[18] Therefore, a washout period of at least two weeks is mandatory when switching to or from MAOIs. A five-week period is required when fluoxetine is switched to an MAOI.[19] A two-week washout period is also required when switching between different MAOIs.

Conclusion

Immediately switching between many antidepresseants appears to be safe and well tolerated, but potentially dangerous pharmacodynamic and/or pharmacokinetic interactions are experienced in some situations, such as the switch from MAOIs to SSRIs, and that from fluoxetine to TCAs. Cross-tapering, an adequate washout period, clinical vigilance and judicious specialist referral are required in these instances.

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