

## Provide optimized antidepressant monotherapy with multiple drugs before considering antidepressant polypharmacy

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**Summary:** Many patients with chronic or recurring major depressive disorder have suboptimal responses to the wide range of antidepressant medications available. When confronted with these patients, clinicians may augment the original antidepressant with other medications, including adjunctive treatment with a second or third antidepressant. Although it is a widely-used practice among psychiatrists and primary care physicians in high-income countries, evidence for the benefits of this type of antidepressant polypharmacy is limited. Care should be taken to utilize this approach only after failure of optimized monotherapy with different classes of antidepressants.

**Keywords:** antidepressants; polypharmacy; augmentation; major depressive disorder; treatment-resistant depression

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Major depressive disorder (MDD) is a chronic recurrent condition. With the advent of efficacious antidepressants in the 1950s and 1960s, the treatment paradigm for this disorder shifted dramatically. There are now a large number of antidepressants with clear benefits in the treatment of MDD, but – given the chronic and recurring nature of this syndrome – many patients have suboptimal responses to these medications. When confronted with these patients, clinicians often resort to augmentation of a primary antidepressant with other medications, including second and third antidepressant medications. Sometimes a second antidepressant is used to target a specific symptom, such as using trazodone or mirtazapine for sleep, but at other times the second antidepressant is to improve the overall therapeutic outcome. While these practices are common, the evidence to support polypharmacy with antidepressants to improve efficacy is minimal.

Combining antidepressants may be useful in some special cases, but there is little evidence to support making this a standard approach for managing

treatment-resistant depression. The potential benefits of antidepressant polypharmacy include potentiation of the partial effectiveness of the initial monotherapy regimen, particularly in resistant depressive cases that show limited benefit from multiple monotherapy switch treatments. Most of the benefit of this type of polypharmacy occurs in individuals with unipolar depression. Various risks of antidepressant polypharmacy include: (a) drug-drug interactions and the impact on medication metabolism; (b) the potential for increased adverse effects, increased rates of treatment-emergent mania, or cycling of bipolar affective patients; (c) increased financial burden; and (d) increased risk of patients' medication errors.

Despite the absence of robust evidence, antidepressant polypharmacy has become commonplace among psychiatrists in high-income countries, particularly among patients classified as 'treatment-resistant' due to failure of multiple monotherapy trials. In a study of office-based psychiatric practices between 1996 and 2006 based on the National Ambulatory Medical Care Survey,<sup>[1]</sup> polypharmacy with two or

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more antidepressants was disproportionately more common among adults 45 to 64 years of age versus those 18 to 44, and it was significantly more common in women than in men. In a separate chart review of 135 patients,<sup>[2]</sup> antidepressant polypharmacy was no better than antidepressant monotherapy in terms of medication response (based on changes in the Clinical Global Impressions Scale (CGI) score), clinical response, or remission rates. This paper also reported that many of the monotherapy trials patients had received prior to 'graduating' to antidepressant polypharmacy were inadequate either in dose or duration. This lends to the concern that general psychiatric practitioners may initiate polypharmacy prematurely, before the effectiveness of monotherapy is fully tested.

The combination of mirtazapine and venlafaxine – termed 'California rocket fuel' – was widely publicized as an effective regimen for treatment-resistant depression. A little over a decade ago, this set off a popular trend among clinicians of utilizing multiple adjunct antidepressants to treat recurrent and severe depression. However, data from the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study<sup>[3]</sup> did not find significantly increased remission rates of patients taking the mirtazapine plus venlafaxine combination versus those on monotherapy with tranylcypromine. However, the side effect profiles and overall tolerability were more favorable with the combination regimen than when using a monoamine oxidase inhibitor. The more recent large-scale Combining Medications to Enhance Depression Outcomes (COMED) study<sup>[4]</sup> again failed to show that antidepressant polypharmacy was superior to antidepressant monotherapy.

The prevalence of antidepressant use among adults in the community in the United States has increased 3- to 4-fold over the last 15 years, reaching an astounding 8-10% of the adult population by 2010.<sup>[5]</sup> Despite the

lack of evidence of effectiveness of antidepressant polypharmacy, as part of this general increase in the use of antidepressants, antidepressant polypharmacy has also increased. Healthplan database reviews in 2011 found that antidepressant polypharmacy was present in 2% of 1615 older adults participating in the health plan and in 3% of 4854 younger adults.<sup>[6]</sup>

Although it is a widely-used practice among psychiatrists and primary care physicians in high-income countries, given the very limited evidence of effectiveness, care should be taken to limit use of antidepressant polypharmacy approaches to the very small number of cases that have failed optimized monotherapy with a variety of antidepressants from different classes. For patients who continue to demonstrate treatment resistance after multiple adequate monotherapy trials, alternative treatment modalities should probably be considered *before* resorting to antidepressant polypharmacy. These alternative approaches include electroconvulsive therapy (ECT), transcranial magnetic stimulation (rTMS), and ketamine, all of which – unlike antidepressant polypharmacy – have shown efficacy in treatment-resistant patients. These alternative treatments have very different mechanisms of action so, unlike antidepressant polypharmacy, they may be able to overcome treatment resistance that develops to conventional antidepressant agents.

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## 抗抑郁药联合治疗之前应考虑各种单药优化治疗方案

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**摘要:** 许多慢性抑郁症患者或反复发作的抑郁症患者对现有的各种抗抑郁药物治疗反应不理想。医生在治疗这些患者时,可能在原来抗抑郁药物的基础上增加其他药物,包括用第二种或第三种抗抑郁药物辅助治疗。虽然在高收入国家这是精神科医生和初级保健医生广泛使用的方法,但是证明这种抗抑郁药联合治疗方法有效的证据不多。只有当不同种类的抗抑郁药物

的单药优化治疗方案无效后,才可谨慎使用联合治疗的方法。

**关键词:** 抗抑郁药, 联合治疗, 增效, 抑郁症, 难治性抑郁症

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