

## When is antidepressant polypharmacy appropriate in the treatment of depression?

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**Summary:** Depression is a serious medical condition that is often only partially improved or completely unchanged after standard treatment with antidepressant medications. Various approaches have been developed to treat this subgroup of individuals with ‘treatment-resistant’ depression; but many individuals continue to live with chronic depressive symptoms that seriously affect their quality of life and overall functioning. One relatively new strategy is ‘antidepressant polypharmacy’ – simultaneously administering two or more antidepressant medications. Given the heterogeneity of the etiology of depression, this approach could improve therapeutic outcomes by concurrently activating multiple neurological pathways with different mechanisms of action, but there is also the risk that using multiple antidepressants would increase the prevalence and severity of side effects. Further work is needed to assess the potential benefits and risks of this strategy to managing treatment-resistant depression.

**Key words:** depression; treatment-resistant depression; antidepressants; polypharmacy; adjunctive treatment; multimodal treatment

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Major depressive disorder (MDD) is a disabling mental disorder with a complicated etiology that involves the interplay of genetic and environmental factors. In addition to the core symptoms of low mood, loss of interest, hopelessness, fatigue, difficulty concentrating, and suicidal ideation or behavior, many patients also have cognitive impairment, moderate to severe anxiety, and other psychological symptoms. Concurrent mental disorders (‘dual diagnosis’) or serious physical conditions are also commonly seen in individuals with depression. Thus, clinical cases of depression are highly heterogeneous.<sup>[1]</sup>

Currently, the most commonly employed psychiatric treatment of MDD is antidepressant medication, which may or may not be supplemented with some form of psychotherapy. However, research over the last decade has indicated that for many patients with MDD one medication is not enough to address the broad range of symptoms they experience as part of their

depressive episode. One major problem in selecting an antidepressant for a patient is that all currently available antidepressants must be administered at the full dose for 2 to 4 weeks to determine whether or not they will be effective. Moreover, remission is only seen for 42 to 46% of individuals with MDD administered the full course of an antidepressant at the full dose, and approximately 30% of MDD patients will not remit even after going through separate courses of treatment with multiple antidepressants.<sup>[2]</sup>

One option for dealing with this problem is to administer multiple antidepressants with different mechanisms of action (i.e., ‘antidepressant polypharmacy’) to simultaneously address the different types of symptoms experienced by the patient and, thus, optimize the treatment effect.<sup>[3]</sup> However, this approach is *not* recommended in the practice guidelines of most countries<sup>[1,3]</sup> which typically recommend the use of a single antidepressant for first-episode depression.

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There are currently few high-quality studies that assess the effectiveness of antidepressant polypharmacy, and the studies that are available are inconsistent. Legitimate concerns about drug-drug interactions that could reduce the treatment effect or increase the prevalence and severity of side-effects – especially among elderly patients – are other reasons clinicians are reluctant to prescribe multiple antidepressants. Due to these considerations, antidepressant polypharmacy is only recommended for patients with treatment-resistant depression who may benefit from the synergistic effect of employing medications that have different mechanisms of action. This rationale based on pharmacological augmentation is highlighted in the recommendations of the American Psychiatry Association's *Practice guideline for the treatment of patients with major depressive disorder*.<sup>[4]</sup>

The earliest evaluation of antidepressant polypharmacy was conducted by Maes and colleagues who compared the effectiveness of monotherapy fluoxetine versus polypharmacy of fluoxetine with either the 5-HT<sub>1A</sub> receptor antagonists pindolol or the 5-HT<sub>2A/2C</sub> and  $\alpha_2$ -adrenergic receptor antagonists mianserin in the treatment of 31 patients with treatment-resistant depression; they found better outcomes in the two polypharmacy groups than in the fluoxetine monotherapy group.<sup>[5]</sup> Another study by Nelson and colleagues<sup>[6]</sup> also found that combined treatment with fluoxetine and the NE reuptake inhibitor desipramine was more effective than monotherapy with either of the medications.<sup>[6]</sup> Similarly, a recent study by Blier and colleagues documented greater improvement among patients with depression who received combined treatment with mirtazapine and paroxetine for six weeks compared to that of patients who received either drug alone for six weeks.<sup>[7]</sup> A subsequent study found that three different antidepressant combinations (mirtazapine + fluoxetine, mirtazapine + venlafaxine, and mirtazapine + bupropion) were more effective than monotherapy with fluoxetine.<sup>[8]</sup> However, one large single-blind randomized controlled study (n=665) – the Combining Medications to Enhance Depression Outcomes (CO-MED) study – did not find any significant differences in the outcomes of patients treated with single medications versus those of patients treated with combinations of antidepressants.<sup>[9]</sup>

Clinicians who consider antidepressant polypharmacy are particularly concerned about antidepressant side effects which could, potentially, increase in frequency, severity, and persistence when multiple medications are being used simultaneously. Earlier work has shown the dangers of severe side effects including the serotonin syndrome when combining tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) or exacerbated TCA-related side effects when combining TCAs with selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and fluoxetine (which is due to increased plasma TCA levels that result when SSRIs inhibit enzymes that metabolize TCAs).<sup>[10]</sup> The concurrent administration of newer antidepressants

with fewer (and milder) side effects may result in a decreased risk of adverse reactions compared to those that occur when combining TCAs and MAOIs of TCAs and SSRIs, but more research is needed to confirm this.

In clinical practice, psychiatrists usually start with one antidepressant. If there is no benefit or the side effects are severe the clinician will change the treatment to another antidepressant. If there is partial benefit and the side effects are relatively mild there are three potential options: (a) increase the dose of the first medication; (b) change to another medication; or (c) augment the first medication with a second antidepressant with an alternative mechanism of action that should, theoretically, improve the treatment effect without seriously exacerbating the side effects. This latter course is the traditional 'multimodal treatment',<sup>[11]</sup> combining compounds with two independent pharmacological mechanisms that complement each other in terms of treatment effect and tolerance. Most currently available antidepressants are, in one sense, already 'multimodal' because they involve multiple pharmacological pathways. Some of these pathways are not directly related to the treatment of depression (which is why they are considered 'dirty' drugs); activation of these non-therapeutic pathways can result in serious side effects when high dosages of the medication are used (outweighing the therapeutic benefit), so in some cases the use of multiple antidepressants can *decrease* the risk of serious side effects because lower dosages of each medication can be employed. For a mental disorder with a complicated etiology like MDD, it is theoretically reasonable to provide combined treatment with two or even three medications with different mechanisms of action.<sup>[12]</sup> Recent clinical evidence has shown that the addition of a 'synergist' (including lithium, atypical antipsychotics, buspirone, and thyroxine) to SSRIs can significantly boost the antidepressant effect of SSRIs; this approach is now considered preferable to increasing the dosage of an antidepressant that is having a sub-optimal effect after being given at full dosage for a sufficient length of time.<sup>[13]</sup>

Antidepressant polypharmacy is another type of multimodal treatment that needs to be compared to the use of a single antidepressant and a synergist; there may be situations in which two different antidepressants result in better outcomes than the use of a single antidepressant and a synergist. It is also possible that different combinations of medications have differential effects on outcomes of interest including: (a) resolution of the core symptoms of depression; (b) rapidity of action; (c) frequency, severity, and persistence of side effects; (d) control of associated (non-depressive) symptoms such as anxiety and cognitive impairment; (e) improvement in social functioning and quality of life; and (f) prevention of relapse. Antidepressant polypharmacy is a potentially important addition to the therapeutic options available for treating treatment-resistant depression, but much more work is needed to clarify the situations in which it will be most useful.

**Conflict of Interest**

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**抗抑郁药物联合治疗抑郁症的时机**

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**概述:** 抑郁症是一种严重的精神障碍, 单一抗抑郁药物系统治疗后往往只有部分患者改善, 有些患者的症状可能毫无缓解。尽管针对这一“难治性”抑郁症患者亚群已经发展出多种不同的治疗方法, 但许多患者仍然带着慢性抑郁症状生活, 生活质量和整体功能受到严重影响。一种相对较新的难治性抑郁症治疗方法就是“抗抑郁药物联合治疗”——同时用两种或两种以上的抗抑郁药物治疗。正因为抑郁症不是单一病因学的疾病, 该方法可以通过同时激活不同作用机制的多种神经通路来提高治疗结果。当然同时使用多种抗

抑郁药物也可能会增加不良反应的发生率及其严重程度。进一步的研究工作将是评估该难治性抑郁症治疗方法的潜在益处和风险。

**关键词:** 抑郁症; 难治性抑郁症; 抗抑郁药物; 联合治疗; 辅助治疗; 多重机制治疗

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