

Prescribing Pharmacotherapy for Major Depressive Disorder: How Does a Clinician Decide?

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Introduction

Selection of treatment according to evidence-based medicine relies primarily on randomized controlled trials and meta-analyses. However, this evidence applies to the “average” patient and ignores the fact that customary clinical taxonomy does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same diagnosis [1].

A rational use of drugs depends on the balance of potential benefits and adverse effects applied to the individual patient [1]. The clinician needs to have a clear account of the potential benefits of a specific treatment, as well as of the predictors of responsiveness and of the potential adverse events that may be triggered by the therapeutic act, which might include side effects and iatrogenic effects. These aspects can only be appraised by clinical judgment, which derives by a refined and comprehensive assessment [2], and not simply by comparing treatment options for the average patient in the treatment of the acute episode of depression and in prevention of relapse,

as it occurs with clinical guidelines [1]. Further, many patients in clinical practice would not be eligible for trials, and this further limits the applicability of guidelines [1, 3].

Potential Benefits

For the treatment of the acute episode of unipolar depression, pharmacotherapy appears to be the most viable strategy for most of the patients who present with a major depressive disorder [1]. Antidepressant drugs offer a number of advantages in specific clinical situations: they are readily available, they can be administered by nonpsychiatric physicians without specialized training, they act in a few weeks.

Psychotherapy (i.e., cognitive behavioral therapy, interpersonal therapy, behavioral activation, problem solving) may yield comparable results [4]. However, compared to pharmacotherapy, it may present a few disadvantages (patients need motivation for psychotherapy; competent psychotherapists may not be available; remission from depression tends to be slower than with pharmacotherapy) [4, 5]. Combined treatment, in particular

pharmacotherapy and psychotherapy, may offer slight advantages compared to each of the treatments alone in the average case of depression. The benefits are, however, clearcut in chronic forms of mood disorders and double depression [4].

If a patient suffers from severe depression there is little doubt that pharmacotherapy may yield substantial benefits, even though, of course, response may vary from patient to patient, and meta-analyses have challenged the notion that the magnitude of benefit compared with placebo increases with severity of depression [6]. However, if symptoms of mild or moderate intensity are present, clinical trials indicate that benefits may be minimal or nonexistent [7].

As important is assessing the stability of symptoms over time. One may postpone prescribing an antidepressant drug and see the patient again after a couple of weeks. If symptoms are mild or moderate and suicidal and/or psychotic ideations are absent or if symptoms have improved to a certain degree, the need of antidepressant drug treatment may be low. In case of persistence or worsening of symptoms, the use of antidepressant drugs appears to be more justified and worth pursuing.

Time to recovery is very individualized, but at least 6 months of drug treatment appear to be necessary for most patients to reach a satisfactory level [8]. This time can be shortened if the sequential combination of pharmacotherapy and psychotherapy is employed [4].

There is a tendency to extend drug treatment for long periods of time, with the assumption that it may be protective against relapse [9, 10]. The evidence supporting this strategy, however, is mainly based on clinical trials where remitted patients were randomized to drug continuation or placebo, without any differentiation between withdrawal and relapse. Withdrawal symptoms following discontinuation of antidepressant treatment are common with any type of antidepressant drugs (but particularly with SSRI and SNRI) [11] and are likely to be misunderstood as indicators of impending relapse [9]. We have no way to know how many of the relapses were actually withdrawal syndromes in the group that underwent drug tapering and discontinuation [10].

Responsiveness

Even when a certain degree of severity is established (a major depressive disorder), the clinical threshold provided by diagnostic criteria can be lowered by the presence of anxiety disturbances. Anxiety and depression coexist

more commonly than thought [12], and this co-occurrence is less likely to respond to antidepressant drugs compared to nonanxious depression [1]. In the setting of comorbidity, that is in the majority of cases, a possibility is that of placing particular emphasis on specific symptoms, instead of simply counting them [1]. For instance, the characteristics that are most predictive of a positive response to antidepressants (e.g., anorexia, weight loss, middle and late insomnia, and psychomotor disturbance) can be given more emphasis than other symptoms. Another important issue is concerned with the primary/secondary distinction of depression that is based on chronology [1]. Secondary depressions which are superimposed on a pre-existing psychiatric disorder (e.g., agoraphobia) are unlikely to fully remit with the use of a single therapeutic agent. Anxiety disturbances may also characterize the residual phase of major depression, which favor residual disability and increase the risk of relapse [12]. Finally, when the severity of a major depressive episode is established, attention should be given to features that may be suggestive of a bipolar course or family history.

An issue that is frequently neglected is the fact that often patients who present with a major depressive episode may have a long history of use of different antidepressant drugs, with frequent switches and augmentation strategies, that may predict reduced responsiveness and/or greater risk of relapse [13]. The term “iatrogenic comorbidity” refers to the lasting effects that previous treatments may entail, well beyond their time of administration [2, 14]. An alternative explanation is that current treatments of depression are simply inadequate in the majority of patients and thus entail a high degree of chronicity.

Vulnerabilities

Vulnerabilities related to antidepressant drugs are generally conceived as the serious and bothersome physical side effects that may ensue with long-term treatment, particularly with SSRI and SNRI, such as gastric toxicity, cardiac problems, bleeding, weight gain, risk of fracture and osteoporosis, and hyponatremia [15, 16]. There are, however, clinical manifestations that may be subsumed under the rubric of behavioral toxicity [2, 17]. In 1968, Di Mascio and Shader [18] specifically addressed the behavioral toxicity of psychotropic drugs. Such a concept referred to the pharmacological actions of a drug that, within the dose range in which it has been found to possess clinical utility, may produce alterations in mood, perceptual, cognitive,

and psychomotor functions that limit the capacity of the individual or constitute a hazard to his/her well-being.

Behavioral toxicity related to antidepressant drugs may be explained on the basis of the oppositional model of tolerance [19]: continued drug treatment may recruit processes that oppose the initial acute effects of a drug. This may explain loss of treatment efficacy and the fact that certain side effects (such as increased appetite and weight gain) tend to ensue only after a certain time. These processes may also propel the illness to a more malignant and treatment-unresponsive course [14], as with bipolar manifestations or paradoxical reactions. When drug treatment ends, oppositional processes may encounter no more resistance, resulting in the appearance of new withdrawal symptoms, rebound symptomatology, persistent postwithdrawal disorders [9, 11], hypomania, or resistance to treatment if it is reinstated. In the long run, antidepressants may increase chronicity, vulnerability to depressive disorders, and comorbidity. The number of clinical studies supporting the oppositional model of tolerance [19] has progressively increased over the years [2].

The Sequential Model

The sequential design is an intensive, two-stage approach, where one type of treatment (e.g., psychotherapy) is employed to improve symptoms which another type of treatment (e.g., pharmacotherapy) was unable to affect [4, 20]. One course of treatment is often insufficient for the complex comorbidities that are encountered in clinical practice and a two-step approach is therefore needed. The sequential design is different from maintenance strategies for prolonging clinical responses that therapies of the acute episodes have obtained, as well as from augmentation or switching strategies because of lack of response to the first line of treatment [4, 20]. The most commonly tested form of sequential design in depression involved use of pharmacotherapy followed by psychotherapy addressing residual symptomatology and/or increasing psychological well-being [4]. It was used in a number of randomized controlled trials and was found to entail significant benefits in terms of relapse rate [21]. Other forms of sequential model involve use of psychotherapy followed by pharmacotherapy, or sequential use of two different pharmacological or psychotherapeutic treatments [20]. The sequential use of psychotherapy and pharmacotherapy deserves more research attention, particularly in forms that are not likely to respond to drug treatment, such as anxious depression.

Practical Considerations

Antidepressants are important and potentially life-saving drugs if the proper indications are endorsed. However, the prescribing physician is currently driven by an overestimated consideration of potential benefits, with little attention to the likelihood of responsiveness and neglect of potential vulnerability to the adverse effects, both side effects and iatrogenic effects, of treatment. Managed health care in underresourced systems may drive the use and overuse of medication and the neglect of psychotherapeutic alternatives.

A rational use of antidepressants that incorporates all potential benefits and harms consists in targeting their application only to the most severe and persistent cases of depression, limiting their use to the shortest possible time. Since behavioral toxicity appears to be related to the dosages of antidepressant drugs, the lowest dose of these agents that seems to be both effective and well tolerated should be employed [2]. Augmenting strategies (i.e., adding new psychotropic drugs to the regimen) need to be carefully weighed, if not avoided, because of their strong link with behavioral toxicity [2].

Antidepressant drugs were developed and found to be effective in the treatment of severe depression, but the better tolerability of newer antidepressant drugs has stretched their original indications. Their use has been prolonged to maintenance and prevention of relapse of depression, under the unfortunate assumption that what made the patient better could keep him/her well, without proper consideration of behavioral toxicity. The sequential use of two different pharmacological strategies (for treatment of the acute episode and for maintenance) has not attracted adequate attention.

Conflict of Interest Statement

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Author Contributions

The authors equally contributed.

References

- 1 Tomba E, Fava GA. Treatment selection in depression: the role of clinical judgment. *Psychiatr Clin North Am*. 2012 Mar;35(1):87–98.
- 2 Fava GA, Rafanelli C. Iatrogenic factors in psychopathology. *Psychother Psychosom*. 2019;88(3):129–40.
- 3 Wisniewski SR, Fava M, Trivedi MH, Thase ME, Warden D, Niederehe G, et al. Acceptability of second-step treatments to depressed outpatients: a STAR*D report. *Am J Psychiatry*. 2007 May;164(5):753–60.
- 4 Guidi J, Tomba E, Fava GA. The sequential integration of pharmacotherapy and psychotherapy in the treatment of major depressive disorder: a meta-analysis of the sequential model and a critical review of the literature. *Am J Psychiatry*. 2016 Feb;173(2):128–37.
- 5 Cosci F, Guidi J, Mansueto G, Fava GA. Psychotherapy in recurrent depression: efficacy, pitfalls, and recommendations. *Expert Rev Neurother*. 2020 Nov;20(11):1169–75.
- 6 Eriksson E, Hieronymus F. The alleged lack of efficacy of antidepressants in non-severe depression: a myth debunked. *Acta Psychiatr Scand*. 2018 Jun;137(6):447–9.
- 7 Braillon A, Lexchin J, Noble JH, Menkes D, M'sahli L, Fierlbeck K, et al. Challenging the promotion of antidepressants for nonsevere depression. *Acta Psychiatr Scand*. 2019 Mar;139(3):294–5.
- 8 Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RM, et al. Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry*. 1992 Oct;49(10):809–16.
- 9 Chouinard G, Chouinard VA. New classification of selective serotonin reuptake inhibitor withdrawal. *Psychother Psychosom*. 2015;84(2):63–71.
- 10 Fava GA. *Discontinuing antidepressant medications*. Oxford: Oxford University Press; 2021.
- 11 Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychother Psychosom*. 2020;89(5):283–306.
- 12 Cosci F, Fava GA. When anxiety and depression coexist: the role of differential diagnosis using clinimetric criteria. *Psychother Psychosom*. 2021;90(5):308–17.
- 13 Amsterdam JD, Kim TT. Prior antidepressant treatment trials may predict a greater risk of depressive relapse during antidepressant maintenance therapy. *J Clin Psychopharmacol*. 2019 Jul/Aug;39(4):344–50.
- 14 Fava GA, Cosci F. Understanding and managing withdrawal syndromes after discontinuation of antidepressant drugs. *J Clin Psychiatry*. 2019 Nov;80(6):19com12794.
- 15 Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs. *Psychother Psychosom*. 2016;85(5):270–88.
- 16 Dodd S, Mitchell PB, Bauer M, Yatham L, Young AH, Kennedy SH, et al. Monitoring for antidepressant-associated adverse events in the treatment of patients with major depressive disorder: an international consensus statement. *World J Biol Psychiatry*. 2018 Aug;19(5):330–48.
- 17 Fava GA, Cosci F, Offidani E, Guidi J. Behavioral toxicity revisited: iatrogenic comorbidity in psychiatric evaluation and treatment. *J Clin Psychopharmacol*. 2016 Dec;36(6):550–3.
- 18 DiMascio A, Shader RI. Behavioral toxicity of psychotropic drugs. I. Definition. II. Toxic effects on psychomotor functions. *Conn Med*. 1968 Aug;32(8):617–20.
- 19 Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry*. 2003 Feb;64(2):123–33.
- 20 Fava GA, Tomba E. New modalities of assessment and treatment planning in depression: the sequential approach. *CNS Drugs*. 2010 Jun;24(6):453–65.
- 21 Guidi J, Fava GA. Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: a systematic review and meta-analysis. *JAMA Psychiatry*. 2021 Mar;78(3):261–9.