

Commentary letter on “Revitalizing monoamine oxidase inhibitors: a call for action”

Carlo Ignazio Cattaneo^{1*} , Michele Fornaro², Francesca Vittoria Ressico¹ and Giulio Perugi³

Letter to the Editor

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Author for correspondence:

*Carlo Ignazio Cattaneo,
Email: dr.carloignaziocattaneo@gmail.com

¹Department of Mental Health, ASL NOVARA, Novara, Italy, ²Neuroscience, Reproductive Science and Odontostomatology, Section of Psychiatry, University School of Medicine Federico II, Naples, Italy, and ³Clinica Psichiatrica, Dipartimento di Medicina Sperimentale- Pisa, University of Pisa, Tuscany, Italy

Dear Editor,

The contribute entitled: “Revitalizing monoamine oxidase inhibitors: a call for action”¹ deserves appraisal about the prescribing pattern in Italy and the lack of further effective interventions besides the monoamine oxidase inhibitor (MAOI) drugs.

New generation antidepressant drugs released within the past decades promoted the selectivity of action, tolerability, and safety issues. At the same time, a new definition of major depression emerged, with broad and blurred boundaries, relegating the most severe forms of melancholic, atypical and mixed-agitated type to the rank of mere “specifiers.” Such a diagnostic shift fostered treatment research in which clinical trials showed an increasingly high rate of placebo response and results that were less and less applicable to clinical practice with the so-called “real-world” patients. Considering that evidence-based medicine (EBM) relies on randomized clinical trials (RCTs), even if limited by selection bias that may reduce their generalizability, international treatment guidelines barely account for older pharmacological agents with no patent-appeal to the brands anymore, and as a consequence, such drugs are less assessed by RCTs.

However, in contrast with the initial idea of a similar efficacy to the previous “less tolerated” drugs, the efficacy expectations of new generation antidepressants have been somewhat disappointed in many instances. Almost half of the major depressive disorder (MDD) patients fail to achieve a response, despite sequential combination or augmentation treatment strategies, irrespective to the operational definition adopted for treatment-resistant depression (TRD)². Figures of non-response or resistance to new antidepressant drugs in bipolar disorder (BD) can exceed those documented for MDD. Resistance can also occur among people treated for an acute manic episode of BD (Fornaro M. et al. “The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials,” submitted for publication). Consecutive treatment failures can either result in acquired tolerance/resistance phenomena, increased risk of suicidal behavior, inflated rates of polypharmacy and healthcare utilization, at least for a subset of more vulnerable patients.

The plea for attention toward the MAOIs made by Gillman et al.¹ seems even more compelling for those prescribing clinicians based in Italy. The last available MAOI for prescription in Italy, namely the nonselective and irreversible inhibitor tranylcypromine, is not available anymore since the year 2018. Its production halted because of poor sales records rather than for safety concerns.

According to the most current report disclosed by the “Agenzia Italiana del Farmaco” (AIFA or Italian Medicines Agency—<http://www.agenziafarmaco.gov.it/en>), even the utilization rate of the tricyclic antidepressants (TCAs) lowered over the time. However, the TCAs still represent a cornerstone treatment for melancholic depression, usually less responsive to new-generation antidepressants³. There are no more secondary amines available in Italy, despite the unquestionable efficacy of drugs such as nortriptyline or desipramine, to name a few.

Worrisome, the availability of the useful (yet quite safe and tolerated) electroconvulsive therapy (ECT) is also very scarce. ECT is available only in 1–2 University Hospital, and 2–3 other public or private facilities nationwide. This is in contrast with all other countries, as covered by the report by Gillman et al.¹, where stable prescription rates of ECT partially counterbalance the lack of MAOIs. While neuromodulatory interventions such as repetitive transcranial magnetic stimulation (rTMS) are gaining popularity even in Italy, there is no conclusive EBM, neither clinical consensus supporting their efficacy for resistant cases of MDD or BD (Fornaro M. et al. “The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials,” submitted for publication).

“*Nemo propheta in patria*” (Latin meaning “no one is a prophet in his/her own homeland”). Regrettably, this statement seems to apply for two Italian clinicians and scientists, Lucio Bini and Ugo Cerletti (1938) who introduced the ECT practice in modern psychiatry, then perfected by fellows and still acknowledged as an undisputed effective intervention worldwide, especially for most severe cases, as endorsed by major treatment guidelines.

Italian physicians rarely prescribe ECT, even for potentially life-threatening conditions such as refractory catatonias. Only a very few residents in psychiatry have the opportunity to train at programs involving ECT. Only a bounce of them has the opportunity to train abroad, where ECT is part of the routine clinical practice, so the chance that severe catatonic states remains undiagnosed and untreated is the rule rather than the exception in our country. No national or international agency seems to place sufficient attention to such a worrisome scenario ultimately endangering the life of many patients.

In conclusion, depression with atypical features has an optimal response towards MAOIs compared to the TCA⁴ or other recently introduced compounds. TCAs are highly effective in the treatment of melancholic depression where both MAOI and new generation antidepressants are less effective. Severe BD depressive patients with prominent mixed, catatonic, and delirious features frequently do not respond to any pharmacological approach, whereas ECT should be considered a first-line option⁵. ECT is an unparalleled intervention even in special situations such as pregnancy, when the use of otherwise highly effective medications such of lithium is discouraged owing to safety concerns (Fornaro M. et al. “Lithium exposure during pregnancy and the postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes,” accepted for publication by the *American Journal of Psychiatry*).

Disregarding established interventions such as MAOIs, TCAs, or ECT, which potential side effects are feasible to manage by experienced clinician sounds like a hazardous attitude with significant public health implications. Unfortunately, nowadays, most of the information on drug treatments reach directly or indirectly doctors through pharmaceutical companies. What is clear is that no pharmaceutical brand will ever solicit for patent-expired medications or ECT. Therefore, we agree with doctors Gillman, Feinberg, and Fochtmann and their co-signatories about the need to favor independent education and improve clinical practice guidelines. International and national agencies, in combination with advocacy efforts, should promote such educational activities in order to assure the continued availability of patent-expired medications such as MAOIs and TCAs, as well as life-saving treatment options such as ECT.

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