Optimization versus early Switching in monopolar depression: A comprehensive review of a clinical controversy

Rodrigo Correa Pulido [1], Rodolfo Philippi Malatesta [2]

In the current management of monopolar depression, achieving functional recovery as early as possible is a challenge that today's clinicians cannot evade, as the delay in symptom remission predicts a higher number of relapses and increased morbidity and mortality. Knowing how to choose, combine or sequence different psychopharmacological strategies, such as optimization or switching of an antidepressant are frequent questions in everyday clinical practice. This reflective review aims to elucidate when the clinician should optimize or switch an antidepressant treatment in a patient with a monopolar depressive episode that goes to a regular appointment after two to four weeks since the onset of treatment and reports partial response to the initially chosen drug. An adequate analysis of symptomatic domains, having a critical view of contemporary clinical guidelines, and maintaining an active but lucid approach at this early stage of treatment are, in our opinion, fundamental elements for the pursuit of an "ad integrum" recovery.

Key Words: *Antidepressants optimization, antidepressants switch, clinical guidelines, antidepressant response*

INTRODUCTION

The risk of early relapse and recurrence reported, as long as residual depressive symptoms remain, has been quantified in numbers reaching 76% in the case of early relapse in patients with residual symptoms vs. 25% probability of the same outcome in those who went into remission. This is evident in everyday clinical practice, but has also been quantified in controlled and naturalistic studies [(1).]

Therefore, achieving symptomatic remission is considered as a minimum requirement when aiming at a functional recovery, as a current therapeutic objective within a modern management framework for a major depressive episode. This process starts with an accurate diagnosis, an adequate selection of pharmacological agents to be used, along with an early optimi-

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1 Psychiatrist. Fellow in Psychopharmacology and Mood Disorders UCSD, USA Head of Mental Health Unit Clínica Santa María. Professor at University of Santiago, Universidad Mayor and Universidad del Desarrollo.

2 Psychiatrist. Master in bioethics and philosophy. Director of PSIFAM Medical Society, Professor at Universidad Diego Portales, Sotero del Río campus.

zation strategy and clinically guided therapeutic options sequencing with support on available studies [2,3].

In this context, clinicians often face a situation in which a patient with a monopolar major depressive episode is checked between weeks two and four, reporting clinical response, but not achieving remission. In the face of this clinical crossroad, we have considered the need to examine the literature for the answer to the following question: Given the need to achieve early remission and functional recovery of the patient suffering from a monopolar major depression and facing a partial initial response: Should clinicians optimize or switch the initially chosen antidepressant treatment? There are limited high quality studies comparing switching strategies vs. dosage optimization, which is a practical challenge for clinical psychiatrists in this stage of the antidepressant treatment. The hereby article will attempt to answer this question following a comprehensive and non-systematic analysis of the available evidence.

Dosage optimization strategy

Optimizing in psychopharmacology terminology involves an increase of the initial dose of an antidepressant until reaching any of the following situations: a) reaching of full doses, b) reaching of doses within the permitted maximum or c) reaching of doses generating such adverse effects in the patient that thus prevent new optimizations. It is a well-known fact that the response to antidepressant therapy usually precedes the remission of a major depressive episode [1], that this remission is in turn highly predictive of a high functional recovery and that the latter leads to significantly less likely relapses [1,2]. However, STAR-D results have been categorical in showing that remission rates are discrete and drastically fall in the third and fourth sequential trials. This, using the vast majority of augmentation, combination or switching strategies, upon which the 36.8% remission rate reached in the initial trial with a selective serotonin reuptake inhibitor (SSRI) is never exceeded [4]. Combinations of high-potency antidepressants from the start versus SSRI monotherapy have shown discrepant results on efficacy in various reports [5,6].

On the other hand, most of the response to an SSRI antidepressant treatment is usually observed at the beginning thereof and as soon as the end of the first week. Thus, the clinical response will continue decreasing during the following six weeks [7]. It is known that optimization achieves its greatest effectiveness when dose increase is conducted by the first and second week of treatment. Thus, it has been shown that the probability of achieving a 50% decrease in HAM-D scores in weeks 1 and 2 of SSRI treatment over placebo, is clearly superior in this short period of time. Then, as the weeks go by, there is a gradual decrease in the magnitude of incremental benefits week by week, even when the drug is optimized [7].

Most clinical guidelines emphasize the importance of achieving early remission, but are unclear in pointing out which antidepressant to start treatment with, and even less so in providing guidelines on the strategy to be followed upon the lack of an early response. It is our opinion that one of the main shortcomings of clinical guidelines is that they fail

to under-classify the various depression types observed in the clinical practice, approaching this construct as “depression” instead of “depressions”. This distinction is not trivial as in clinical practice, it is the sub-type of depression and groups of predominant symptoms or “target” symptoms which seem to guide the prescription of more experienced psychopharmacologists.

From the point of view of a clinically guided choice of a first antidepressant, factors to be assessed are all known: treatment history and individual and family response, predominance of symptoms spectrum, episode severity, patient preference, side effects profile, safety, medical and psychiatric comorbidity and tolerability. Faced with partial response but high tolerance upon 2 to 4 weeks of treatment, the World Federation of Biological Psychiatry Societies proposes an optimization of the first drug to the maximum permitted doses. In fact, in view of symptoms’ persistence in subsequent checkups, other types of potentiation are recommended prior to switching (use of atypical antipsychotics, lithium or other strategies) or combining antidepressants with synergistic mechanisms of action (adding mirtazapine as an example) [8].

There are high quality double-blind controlled trials proving that early optimizing doses is more effective than switching to another antidepressant. This is well documented in the work of Kudlow, where he thoroughly analyzes the studies of Bosé and Romera, both of 2012, which report that an increase in escitalopram from 10 to 20 mg. vs switching to duloxetine early dosed at 60 mg in two weeks for no-responders, did not result in statistically significant differences at 8 weeks checkup [9].

On the other hand, there are common sense clinical factors supporting optimization vs. switching in the face of a partial response. Thus, for instance, when conducting a medication change, patients are more likely to show new side effects, become suspicious of treatment and possibly show therapeutic delays when starting with a second antidepressant. The latter is highly significant if the second drug does not share effects in at least some common monoaminergic system with the initial antidepressant.

What is clear in all reviews and studies is that an early therapeutic change is required if a response in excess of 20% has not been reached by the second week over the scores gathered at baseline. If a therapeutic adjustment is not designed, only 1 in 5 patients will achieve a clinical response (over 50% recovery) in eight weeks of treatment. There is no consensus on the most appropriate time to conduct this therapeutic adjustment in the research, but most of the evidence suggests that it should be conducted between weeks 2 and 4 of treatment [8].

Antidepressive therapy switching or replacement

The last data provided in the previous section is highly relevant, as it shows that the lack of an early improvement, as defined by a symptomatic decrease of less than 20% on a standardized scale for depression in weeks 2 to 4 of treatment, will be predictive of a clinical non-response in week 8 of treatment (8). In this case, an optimization strategy could be unfortunate, and looking for other mechanisms of action, better shaping the patient or

looking for more tolerable collateral effects would be a more reasonable way to proceed.

It is conceptually important to define that making a switch means replacing the drug used in the first line to another antidepressant of the same or different class. Although there are no solid data on the use of a second drug of the same class than that which did not achieve early improvement, it is related with lesser results over switching to a drug of a different type, most of the "switches" performed by expert psychopharmacologists are towards molecules of other kinds which enable the recruitment of a greater number of monoamines.

The group led by Haro et al., trying to answer the question: Which patients would benefit the most from switching?, conducted the "PERFORM" observational monitoring study from 2011 to 2015, in 5 countries in Europe and involving the recruitment of 1402 patients.

The goal was to better understand the course of a depressive episode and its impact on the functioning of a patient in a 2-year follow-up. It was also sought to learn about the clinical profile of patients in which antidepressant switching is indicated over the group of patients who maintain the same antidepressant selected in the first line. The sample was split into 910 patients beginning on an antidepressant (78.7%) and 247 patients who were switching (21.3%).

The profile of the patients in whom switching was conducted can be observed in Table 1, and differs in multiple characteristics over the group initiating and maintaining the same antidepressant. Patients with the greatest symptoms severity, presence of anxiety, painful symptoms, side effects with the first drug, impacts on quality of life, old age, widowed, or divorced were switched to another antidepressant with a greater probability [10].

Variable	Switch	First Antidepressant attempt
Severity of depressive symptoms	Major	Minor
Anxiety	Major	Minor
Impact on quality of life	Major	Minor
Impact on global functionality	Major	Minor
Probability of suffering from chronic pain	Major	Minor
Side effects of the first drug	Major	Minor
Previous use of health resources	Major	Minor
Formal education	Minor	Minor
Adverse effects to first line drugs	Major	Minor
Age	Major	Minor
Probability of being widowed, divorced / separated	Major	Minor

The focus of the discussion is then that cohorts of patients who will require switching antidepressants will have differential clinical characteristics over those who will respond to a first attempt pharmacological trial. Haro's study proves that we should conceptually think of "depressions" as a group of entities with distinct symptoms and treatment responses.

When analyzing the main causes for switching, the following was found: lack of efficacy (77.3%), adverse drug effects (9.3%), patient choice (6.9%) and lack of "compliance" (3.2%) (10). Similar conclusions were obtained in 2012 by the Saragoussi group, who reported that 72% of antidepressant replacements occurred within the first three months of treatment and especially affected more severe patients (previous depressions, psychiatric comorbidity or prominent anxiety symptoms) (11).

In an interesting Japanese randomized controlled double blind study called "SUN-D", 2013 patients were recruited in 48 hospitals between 2010 and 2015. The methodology consisted of a double randomization. Thus, patients were split into four study arms. The first arm consisted of initiating and maintaining patients with sertraline 50 mg daily (n = 970). In the second study arm, a group of patients was rapidly indicated sertraline 100mg daily (optimization) (n = 1041). The second randomization covered study arms 3 and 4. A switch to mirtazapine in a dose of 7.5 to 45 mg per day (n = 259) was made in the third arm, and a combination with mirtazapine in a dose of 7.5 to 45 mg per day (n = 286) was conducted in the fourth arm. This second randomization was conducted upon three weeks of treatment in those who had not achieved remission, and a results assessment was agreed upon at 9 weeks of follow-up (12).

The study's results are interesting as they show that there were no significant differences between weeks 3 and 9 in the patient's health questionnaire scores (Patient Health Questionnaire, PHQ-9) and Beck's Depression Inventory (Beck's Depression Inventory, BDI) when comparing both doses of sertraline in the first randomization which methodologically simulates a dose optimization strategy. This is consistent with at least two randomized controlled studies reporting no advantages of optimizing doses with sertraline. The first one optimized from 50 mg to 150 mg upon failing to respond in week three of treatment (13) . The second one reported no progress when optimizing sertraline from 100 to 200 mg upon six weeks of treatment (14). Similarly, a systematic review published in 2005 showed, by direct evidence, that the use of SSRIs at high doses was not related to an increase in treatment efficacy (15).

Results obtained in the second randomization were expressed in number necessary to treat (NNT) and report that the NNTs from switching to mirtazapine were 12.2 for response and 11.9 for remission. A combination thereof obtained even better results, with an NNT of 11 for response and 8.1 for remission. Following this second randomization, there was a slight increase in side effects with an abandonment of treatment ranging from 6 to 8%. These findings lead the author to conclude that switching and combination strategies are superior in obtaining responses and remission over early dose optimization with sertraline.

The fallacy behind the apparent certainty of clinical guidelines

One of the most frequent contemporary trends in psychiatry is making clinical decisions based on recommendations from various international guidelines. Probably, the main reason why this occurs is because, for many mental health professionals, this type of document stands at the highest standard of evidence available, free of bias and including consistent and useful information for everyday clinical practice. However, in an excellent report by MacQueen et al. 21 clinical guidelines worldwide are analyzed in a systematic way. The above, in order to learn on the quality of the information contained and critically assess recommendations made in the event of failure of a first antidepressant trial (16). An instrument known as "AGREE II" was used for this purpose, which is specially designed to quantify the quality of a clinical guideline in the following seven domains: 1) scope and purpose, 2) involvement of interest groups, 3) thoroughness in the guideline development, 4) presentation clarity, 5) applicability, 6) editorial independence and 7) general assessment. A relevant finding of this report is that the large majority of the 21 analyzed guidelines, showed indexes less robust in AGREE II in the following items: involvement of interest groups, thoroughness in the guideline development and editorial independence. On the other hand, only 8 guidelines define "response" as a 50% reduction of depressive symptoms and "partial response" as a 25-50% reduction of depressive symptoms. Of these 8 guidelines, only 3 suggest different treatments for those with a partial response vs. those without response to a first pharmacological trial. Thus, the remaining 13 guidelines do not provide any operational definition of inadequate response. As additional data of interest, it is reported that only the New Zealand guideline was made with the "scope and purpose" of being used by psychiatrists; the remaining 20 guidelines were designed for physicians non-specialized in mental health.

Finally the fact that none of the 21 clinical guidelines refers to what type of antidepressant was used in the first line when a recommendation is made in the second line is highly important. A clear example of this are the CANMAT guidelines, which provide recommendations in 2nd and 3rd lines, but these are very broad, including various strategies of both combination and augmentation. Thus, all clinical guidelines designed for depression and analyzed in this report do not clearly respond to the question: What is the best second line choice when there is partial response or lack of response following a first antidepressant trial?

Finally, one of the ideas most widespread by these type of guidelines is the use of SSRI antidepressants as the first therapeutic line in major depression. The poor quality results of these guidelines, the frequent lack of an operational definition of "response" versus "partial response" versus "no response", in addition to the lack of precise recommendations in the second line, require a critical rethinking for the idea of systematically using an SSRI antidepressant in the first line. Perhaps the most clinically lucid manner to handle this type of dogma, is the idea of directly seeking and addressing what are known as "target symptoms" or predominant symptomatic groups at the clinical instance

of each patient and then, depending on such, choosing a first antidepressant to use (17).

DISCUSSION

An adequate analysis of symptomatic domains from the first consultation in order to achieve early improvement and remission, in addition to functional recovery, is a contemporary imperative in the handling of depressive patients. In this sense, the non-systematic literature analysis naturally leads to question the rather dogmatic and rooted idea of always starting treatment with an SSRI.

The evidence shown allows deducing that early optimization has good results with a low risk of adverse effects, in the face of a response that is between 20% to 50% in a first checkup, following the commencement of an antidepressant. On the other hand, switching will make clinical sense when early improvements of more than 20% of symptomatic reduction below the baseline are not achieved. In these cases, we should ideally consider a new class of antidepressant, other than the one used in the first instance, and select a molecule with the best side effects profile, using what is known as “target symptoms strategy”.

Regarding early optimization efficacy, it varies greatly depending on which antidepressant treatment is chosen in the first line. The available evidence reports that early SSRI optimization efficacy when there is no response over than 20% within the first three weeks, is scarce. This is consistent with the fact that dose increases do not capture new monoaminergic systems and could eventually cause side effects derived from 5HT1A receptors.

On the other hand, optimizing a dual antidepressant such as venlafaxine adds various mechanisms of action as the doses increase, thus being able to capture more monoaminergic systems, which would result in a higher probability of early remission. This optimization effect is also observable with tricyclic antidepressants and mono-amino-oxidase inhibitors (MAOI), but in these cases, therapeutic windows prior to generating side effects which result in discontinuation, must be seriously considered. The entry of designer drugs such as the multimodal antidepressant vortioxetine or vilazodone a serotonin partial agonist reuptake inhibitor (known in nomenclature as “SPARI”), and in which dose / response linearity has been demonstrated, open new and interesting routes in the search for an early remission and functional recovery.

CONCLUSIONS

Early optimization has proven to be an effective strategy in the achievement of early remission and functional recovery, which is in turn a solid predictor of the lack of an early relapse and recurrence. In the choice of the first drug to be used, safety and a low side effects profile is essential to avoid abandoning treatments and therefore future relapses.

Early optimization, upon two to three weeks of treatment onset, in initial responders who did not remit, is the first strategy to be used. Waiting six to eight weeks for the “full effect” without dose adjustments, can be nowadays considered as an unacceptable anachronism, since it significantly delays patient remission and functional recovery.

Switching or combination is recommended in the second or third week of treatment if there is less than 20% improvement over the baseline, or if, in the fourth week, having conducted optimization, there is no clinical response (50% improvement over baseline).

A correct conceptualization of the patient profile and a first line choice based on the concept of target symptoms, thus choosing various mechanisms of action such as: multimodal effect, specific serotonergic and noradrenergic effect (NaSSA), dual action mechanism (SNRI) or the use of an SPARI antidepressant will most likely achieve earlier remissions over the dogmatic use of an SSRI. The above, given the high heterogeneity in clinical expressions in the group of depressions. Finally, monitoring side effects and comorbidity profile in these drugs will be essential to improve patient adherence, an essential factor in functional recovery.

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Mailing at:

rcorreap@gmail.com and/or
rphilippimalatesta@gmail.com