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Guest Editorial / Misafir Editoryal

Evidence Based Criteria for the Antidepressant Choice

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INTRODUCTION

Antidepressant drugs are, according to some estimates, the most widely prescribed class of drugs in the population with 253.6 million prescriptions in 2010 in the United States of America (1). This capacity is due to a number of factors including a wide range of indications and an overall good tolerability. Therefore antidepressants are currently prescribed very frequently by physicians, also recommended by non psychiatrists.

The success of antidepressants led to the development of many new compounds over the last decades and we are now able to use more than 40 licensed compounds licensed in the treatment of depression.

The availability of so many compounds is positive on one hand, because of the possibility to choose within a wide range of different compounds; but on the other hand it causes confusion for the clinician, who may not be aware of the differences across so many apparently similar drugs. As a result, in the clinical practice many psychiatrists usually prescribe only a small number of compounds which they are familiar with and never or seldom take into consideration other compounds. It is not exceptional to encounter colleagues who prescribe just 2 or 3 different antidepressants, therefore neglecting a wide range of other compounds which could be better suited for their patients.

Therefore, the big challenge, which is the main aim of this editorial, is to solicit the awareness within psychiatrist of the whole range of therapeutic possibilities that we have. In fact, on the contrary to what is currently believed, antidepressants are very different one from another and the selection should be performed with great care taking into consideration a wide range of evidence based factors.

The Choice of the Antidepressant

The choice of the best compound for each patient is always a very difficult procedure. In a very short period of time during the interview with the patient, we have to choose best suited antidepressants, among many compounds taking into consideration a large number of factors such as symptomatology profile, previous efficacy, medical comorbidities, subject preferences, family history and so on.

As an example, the specific symptomatology profile of the patient is important in the choice of the compound. A patient with predominant sleepiness and apathy will probably benefit less from mirtazapine than fluoxetine. But then, a patient with prevalent anxiety and insomnia will benefit more from mirtazapine than fluoxetine.

Also, the information about previous treatments is very important: if a specific compound was effective in a past depressive episode, this is the main criterion to

use the same compound in the present episode of depression. Therefore it is crucial to specifically ask the patient about previous treatments and their effectiveness. If other members of the family suffered from depression, it is important to know how they were treated and the outcome of treatment, as family members share a relevant part of their genes. Therefore a positive outcome in one member of the family may be an indicator of good efficacy for same compound, in the patients that we are treating (2).

The presence of medical comorbidities is another very important criterion for the choice of a compound that is not interfering or, even worse, aggravating the medical condition. Further, in case of medical comorbidities, it is very frequent to observe subjects taking a large number of medications, and this raises the issue of drug-drug interactions, which should always be taken into serious consideration to avoid dangerous side effects.

Finally, we should always remember to ask the patient about specific preferences. As we will see later on, all antidepressants have a range of side effects, and some of them are more or less tolerated by different subjects. As an example, sexual side effects could be very worrisome for young and married subjects and less for other subjects not sexually active.

The process of matching the profile of the patient with all different profiles of available compounds is therefore quite complex. The consequence is that pharmacologic treatments usually follow a trial and error procedure. A common sentence that clinicians say to the patient is: "let's try this compound for a few weeks and let's see if it is useful for you and well tolerated". Unfortunately, this strategy frequently leads to huge loss of precious time and to a much-reduced compliance by the patient, which in some cases has been demonstrated to be more than 50%. In other terms half of the subjects quit the treatment spontaneously in the first few weeks of treatment and this could be avoided or reduced with a careful choice.

In the recent years, the use of prescribing guidelines became more common also because of the risk of legal actions and patients' sue. Unfortunately, guidelines are not so effective in such a complex and detailed choice. Guidelines are in fact mainly suggesting the use of classes, and differences across single compounds are not usually reported, or if they give specific suggestions, it is too small extent (such as the Canadian Network for Mood and Anxiety Disorders-CANMAT guidelines) (3). Therefore, clinicians were left alone, most guidelines suggest the use of serotonin reuptake inhibitors as a first line of treatment for depression but they do not go into detailed underlining and explaining the differences across each compound. In this way, the clinician usually chooses the compound on the basis of personal opinion, past experiences or informations or even worse on the basis of marketing pressures.

In the recent years, due to the awareness of the need for more precision medicine, rose emerge to a number of initiatives aimed to help clinicians to choose the best treatment for each of their patients.

Evidence Based Precision Medicine

Precision medicine intends to offer to clinicians the possibility to tailor the treatment according to the best possible evidence of effectiveness and tolerability for each subject. This aim is to be reached through a number of tools ranging from biologic measures to observable clinical features. The task is challenging because of the complexity of psychiatric disorders which biological determinants are only partially known. Biological predicting factors, including genetics, will probably be the future of precision medicine; because we know that more than 50% of the antidepressant response is controlled by the genes. However, at present, there are only a few objective findings in this field and we cannot consider the possibility of a widespread the routine use of genetic tests for antidepressant prescription yet (4,5).

Therefore at present, we can focus on precision medicine by using the evidence-based findings that we have at a clinical level. This is exactly the aim of a very large project named: Precision Medicine Initiative (6). This is a huge study, aiming to recruit one million subjects treated as usual. Within the scope of study, large number or information and clinical variables will

be collected in order to analyze which clinical variable or combination of clinical variables combined also with demographic features predicts a better outcome, during psychiatric therapy.

This study, together with the use of big data, which are the large amount of data that are routinely collected from electronic medical records in many hospitals, electronic health records, that routine in many countries, will allow an unprecedented evidence-based knowledge about the criteria for targeted prescriptions. However, at present, we have a lot of useful information which should be already used but which is probably not completely known by all clinicians.

Which Antidepressant is the Most Effective?

In the previous sections, we discussed the possible differences across compounds, but is any antidepressant is better than the others? In other words, which is the most effective antidepressant? All patients ask for the most effective antidepressant and, similarly, all clinicians would like to offer to their patients the most effective compound. Therefore, in the recent years, many studies aimed to identify the most effective antidepressants. One of the most influential studies is a network meta-analysis published a few years ago (7). In this study all antidepressants were ranked based on their efficacy and tolerability, however results initiated some discussions. My personal opinion; ranking, which is reported in the paper, is not completely useful for clinicians, and probably it is misleading because of some antidepressants is better than others. However, when looking carefully into the results, anyone can observe that the differences between the overall efficacy and tolerability were very small and not clinically significant (Odds Ratios were 1.2-1.5). Statistical significance probably depended on a large number of patients and the individual differences that we mentioned above, were lost in an average effect. Even if the overall effect of antidepressants are similar, they are different in their specific profile, which makes them more fitting to specific patients compared to others. We can't see this effect in large samples. In fact, it is a common clinical experience, that no overall best antidepressant exists. Each compound has a unique and specific efficacy and tolerability profile based on a unique pharmacodynamic profile. As an example, in the study by Cipriani et al. (7), mirtazapine resulted to be the best antidepressants, but we all know that mirtazapine specific pharmacodynamic profile is causing sedation and weight gain in most cases. Therefore, mirtazapine is not generally indicated, for example, in cases with atypical depression which is characterized by hypersomnia and increased appetite. In conclusion, there is no best antidepressant.

Tolerability as a Guide for Individualized Treatment?

We have seen that there is no best antidepressant and a number of criteria can be used to an evidence-based individualized choice of the best compound for our patients. Probably the most useful criterion for selection is the detailed information about the tolerability profile of each compound.

Unfortunately, none of the antidepressants is completely free of side effects. Therefore the careful evaluation of the best tolerability profile is probably the biggest part of precision medicine, currently, we may use in the clinical practice. Commonly used antidepressants are generally well tolerated but they present a range of side effects. Frequent side effects are not severe but may impair compliance in our patients, in other respects less frequent side effects may be severe, sometimes.

With this in mind, in the recent years, various meta-analyses with the aim of offering to clinicians information about the degree of tolerability in different areas of the antidepressant compounds were performed.

Probably one of the most important criteria is the differences that we have regarding the effects on sleep. An interesting Italian, unpublished, study questioned 1000 psychiatrists about the sedative or activating profile of currently available antidepressants. Results were somehow very surprising: for each compound, there were psychiatrists believing that it was activating and other psychiatrists believing that it was sedative.

The most extreme and interesting finding was related to paroxetine. In this case half of the interviewed psychiatrist reported that paroxetine is sedative while another half reported that in their experience paroxetine is indeed activating. This in fact is not surprising because it is a common experience. When we talk with our colleagues, that it is very common to hear very different opinions on the same compounds. This is a reason, why there is the need of evidence-based data, that can give clinicians objective information for their everyday clinical practice.

In a recent meta-analysis, authors reported a clear ranking of antidepressants regarding their sedative and activating profile (8). Some results were obvious, for example for bupropion, which resulted in being an activating antidepressant, and for mirtazapine, which resulted in the most sedative one. However, for other compounds, the ranking is useful for guiding clinicians' choice.

Similarly, another very large meta-analysis provided evidence-based information about the sexual side effects of antidepressants. In this study, it was clear that many antidepressants have a significant impact on the patient sexual functioning. This impact is it spread in all the three phases of desire, activation, and orgasm. However, compounds differ greatly, with some of them causing relevant dysfunction, for example, venlafaxine, paroxetine, sertraline, and citalopram, while others, such as bupropion or escitalopram having a much lower impact on sexual function (9).

Weight gain is another important common side effect of antidepressants and the large majority of psychiatric medications. Patients very frequently are concerned about weight gain and it is a common reason for the lack of compliance, not to mention metabolic consequences. Also, in this case the compounds differ considerably, with paroxetine and mirtazapine being the ones causing higher weight gain and others such as bupropion and fluvoxamine having a much more neutral effect on weight (10). Detailed information of the tolerability profile of each antidepressant is extremely important for personalize treatment.

How can We Use Evidence-Based Information for an Antidepressant Prescription?

According to information that, we have summarized above, it is very clear to understand how complex is to combine all the needed information in a short period for prescribing the antidepressant, when we meet our patients. Therefore, it would be very useful to have some informatic support, such as some algorithm which can combine all the information available for the specific patient, a short list of medications that we can choose based on our knowledge. At present, a number of attempts are made for this purpose, but none of them is clinically available yet.

The only option we have, at the present time, is to be updated about the evidence available for each antidepressant. Their tolerability profile, interaction and pharmacodynamic properties are important in order to select the best antidepressant for each of our patients considering their history and preferences.

Conflict of interest: Dr. Serretti is or has been consultant/speaker for: Abbott, Abbvie, Angelini, Astra Zeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier.

Link to youtube presentation: https://youtu.be/0MLtpsXl-Fo

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