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MYTHS SURROUNDING THE LATENCY OF ACTION OF ANTIDEPRESSANT THERAPY

Summary

Objectives: Major Depression after anxiety disorder, is the most common mental disorder in the world. Studies conducted on quality of life have shown that depression causes the greatest disability and most lost days of work compared to other physical or mental disorders.

Materials and methods: To date, it has not been possible to identify biomarkers that are capable of predicting in advance a response to antidepressant drugs. If it was possible to develop criteria to facilitate a more rapid identification of an effective drug treatment, there would be obvious advantages: it would shorten the length of patient suffering and would reduce lost treatment time spent on ineffective drug treatments. Several studies have analyzed the predictive value of the initial response to antidepressant drugs and it has been found that an improvement of the Hamilton Scale of 20%, 25% or 30% after 2 weeks is a positive predictor of outcome after 6 weeks.

Results: Therapeutic Drug Monitoring is the measurement of a specific drug serum concentration to ensure that appropriate drugs levels are maintened. For every drug it is possible to delineate a specific "Therapeutic Index," a ratio between the toxic and therapeutic doses of medications.

Conclusions: Prediction of Antidepressant Response can be improved by a combination of early response assessment and plasma drug monitoring.

Key words: Prediction of antidepressant response; onset of antidepressant response, Therapeutic Drug Monitoring (TDM)

Introduction

Depression after anxiety disorder, is the most common mental disorder in the world. The incidence of depression in women is double that in men. There are case reports describing depression in children as young as 3 years of age; there are prevalence studies on depression that include children from 7 years of age [1]. Depression is currently ranked as the fourth leading cause of disease burden worldwide and it is estimated that by 2020, it will be second only to cardiovascular disease as the leading cause of disability [2].

According to the World Health Report 2001, published by the World Health Organization (WHO), neuropsychiatric disorders are among the diseases with the most serious psychosocial implications (DALY = disability adjusted life years). Of these, depression is the disease that affects the greatest number of years of life (WHO 2001) [3]. Studies conducted on quality of life have shown that depression causes the greatest disability and most lost days of work compared to other physical or mental disorders [4]. It is estimated that between 40 and 70 percent of people who commit suicide suffer from depression and that the risk of suicide is 20 times higher in depressed people compared to the general population [5-7].

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In depression, quality of life impairment correlates with symptom severity [8]. 50-75% of patients suffering from depression obtain adequate remission of symptoms [9 10]. However, some patients have persistent residual symptoms, of which anxiety is the most frequent symptom [11 12]. 20-30% of depressed patients show an immediate response to drug therapy [13], while only 10-20% obtain permanent remission [14]. The high incidence of incomplete response carries an increase risk of relapse [15]. Recent research shows that only a third of patients respond to the first antidepressant drug prescribed (33%), another third to the second (24%), 7% to the third and only 4% to the fourth (Gaynes et al. 2008) [16]. The probability of obtaining remission after only 6 months is reduced already by 50%. After nine months it further reduces to 15%, then it reduces to approximately 1% for each month thereafter [17 18]. The duration of the depressive episode seems to consistently correlate with clinical response and efficacy of antidepressant treatment; for this reason the issue of latency of antidepressant action is of fundamental importance.

Antidepressants are commonly prescribed using a "trial and error" approach. To date, it has not been possible to identify biomarkers that are capable of predicting in advance a response to antidepressant drugs [19]. According to widespread opinion, antidepressant treatment must be taken for at least 2-3 weeks and up to a maximum of 6 weeks in order to achieve the desired clinical effect. In long standing depressive episodes, the latency of action can be prolonged for 8-10 weeks old, if not longer [20 21]. By adhering to the "Texas Algorithm" [22], defined on the basis of a study that evaluated the effectiveness of using an algorithm-driven treatment (ALGO) compared with treatment as usual (TAU) in depressed patients, it follows that a period of time as long as six months may have passed from the first drug prescribed in stage 1 to the treatment option in stage 4. If it was possible to develop criteria to facilitate a more rapid identification of an effective drug treatment, there would be obvious advantages: it would shorten the length of patient suffering and would reduce lost treatment time spent on ineffective drug treatments. It would also lead to more rapid optimization of drug therapy and would facilitate decisions on whether to increase or replace medication. Although some treatment guidelines indicate that the latency of action of antidepressants is shorter in non treatment resistant patients, the majority of them do not indicate any strategies aimed at optimizing treatment intervention; rather the advise is to wait and not make any drug changes before 4-6 weeks (Table I). These recommendations are based on the findings of placebo-controlled studies, where differences in response were only seen between the third and fourth week of treatment. This analysis led to the conclusion that an early response is mostly related to a placebo effect and a poor clinical improvement later.

By using this temporal pattern in the treatment of depression, other therapeutic treatments may be adversely effected, especially if symptoms such as lack of pleasure, initiative and interest persist. These residual symptoms represent an additional challenge to treatment. A drug perceived as ineffective may undermine a patient's motivation and therefore may cause early interruption of treatment, which carries not only an increased risk of suicide, but also of chronic illness and disability.

With recent neuro-imaging techniques, it now seems possible to identify those patients who are more likely to respond satisfactorily to antidepressant therapy. In a recent review [24] the authors highlight that in some MRI studies, larger volume in the hippocampus and the cingulate gyrus correlated with a greater tendency towards clinical remission.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging tool where it is possible to construct three-dimensional biomedical images by exploiting the tendency of water molecules to move in an isotropic manner, meaning in one direction, due to the presence in biological tissues of barriers such as cell membranes. Using this technique, it has been demonstrated [25] that depressed patients who fail to obtain satisfactory clinical remission with SSRI therapy, have abnormalities in the white matter of the right amygdala while in contrast, the left amygdala and the hippocampus bilateral connections are not compromised. According to some authors [26], it is possible

Table I. When to consider changing drug therapy [22 23].

After 4 weeks, assessment of clinical response to pharmacological treatment, in order to optimize dosing.
Subsequent assessments at **8, 12, 16 weeks**.
Three possible treatment responses:
- Full Response
- Partial Response
- No Response

In the case of Full Response: continue drug therapy for al least 6 months
in the case of Partial Response: consider risk-benefit treatment factors
In the case of No Response: change of drug therapy recommended

using DTI to predict vulnerability to suicide behavior in euthymic patients with a history of depression.
A study investigating DTI in elderly depressed patients [27] showed the presence of reduced anisotropy in the white matter of various corticostriatal-limbic regions.
Some research has documented evidence of pharmacological efficacy within two weeks of treatment for several classes of antidepressants. In several studies the Stassen Group [28-30] have shown that an initial reduction of 20% of the Hamilton scale (within two weeks) is followed by a later clear and stable therapeutic response. Conversely, a lack of improvement in the first two weeks can be interpreted as a negative predictor of response. Also, by stratifying the sample of patients according to severity of symptoms at illness presentation, it was shown that response to drug therapy was related to the severity of depression (the more severe the symptoms at onset, the more consistent and rapid the extent of clinical improvement). Several other studies [31-36] have analyzed the predictive value of the initial response and it has been found that an improvement of the Hamilton scale of 20%, 25% or 30% after 2 weeks is a positive predictor of outcome after 6 weeks. Following on from these studies, Szegedi [37] introduced the concept of stable remission, defined as a 50% improvement of the Hamilton Scale Score, detected after 4 weeks and that persists after six weeks. Using the narrower criteria of stable remission, the percentage of patients obtain remission is reduced.
These results have been confirmed by further research conducted on over 6,000 patients [38 39] and included studies on tricyclic and tetracyclic antidepressants (TCAs: imipramine, amitriptyline, maprotiline), SSRIs (fluoxetine, paroxetine), NaSSA (mirtazapine), the reversible MAO-A inhibitor (moclobemide) and substance P antagonists. It has been postulated that antidepressants have a class effect and that no significant differences in efficacy exist among drugs in the same class, evidenced in part by number needed to treat analysis. This research further reinforces the idea that antidepressants have a class effect with regard to efficiency and latency of action.
It has been suggested that early response to treatment may be due to a placebo effect [40 41], for example, due to an implicit bias created by the increased attention paid by the investigators towards a patient during the early stages of the study. To help over come this problem, Gomeni [42] developed a statistical analysis that identifies placebo responders on the basis that their scores appear to be approximately double for a defined percentage of items of the Hamilton Scale.
Overall it can be assumed that if a patient fails to show any clinical response during the first two weeks of treatment, then the probability of obtaining an improvement is only 15% and this reduces further to 8% after three weeks. There is a small group of patients (on average 8%) where no improvement is detected after three weeks but they may still respond to drug therapy. In any event, the practice of treating patients for a long period of time in the absence of any initial improvement and without using a more assertive pharmacological treatment approach, needs to be questioned.
On the basis of these observations, a Working Group coordinated by Hans Stassen and supported by Jules Angst formulated the following guidelines:

Aim to prescribe an appropriate therapeutic drug dose within a short period of time;
If there is no sign of clinical improvement after 10 days, then:

- Increase the drug dose, or
- Choose an augmentation strategy

If after 3 weeks there is no improvement, then consider changing drug.

“Of course, these are only general guidelines and must be adapted to the clinical needs of the individual patient” (Jule Angst)”.

This advise appears to contrast with other recommendations on the prescription of antidepressants that promote a “start slow and go slow” approach and before being applied other important factors that influence drug prescribing must be considered, for example, illness severity, comorbidity, age, tolerance and treatment setting (inpatient or outpatient).
Other international research has shown that applying empirically based, systematic treatment algorithms, especially in an in-patient setting, can significantly reduce both the period of hospitalization and the number of drug prescriptions, resulting in greater patient satisfaction as well as professional satisfaction amongst colleagues (Conca 2007, unpublished results).
To achieve more optimal drug prescribing more attention should be paid to a drugs efficacy profile as well as to its side effect and safety profile, which in turn requires a more thorough understanding of the different classes of antidepressants. In terms of side effects, there are obvious differences between individual drugs: for example, the cardiotoxicity of TCA

and its significant anticholinergic side effects such as dry mouth, constipation and visual disturbance.
Informed and selective prescribing that takes into account both the side effect profile of a drug and the individual symptoms of the patient, leads to improved compliance and more effective treatment of the depressive disorder; residual symptoms such as lack of motivation, somnolence, ecc. may benefit from the combined intervention of prescribing an SSRI with a NDRI (e.g. bupropion).
Plasma drug monitoring or "Therapeutic Drug Monitoring" can optimize and individualize the different stages of treatment, provided it is used correctly [43]. It is a valuable tool has been used now for a number of years in everyday clinical practice for the optimization of pharmacotherapy and consists essentially of the measurement of plasma drug concentrations to inform eventual dose adjustments. For example, in the case of SSRIs, recent studies [44] using PET imaging of different regions of the brain, have shown that plasma concentrations have a positive correlation with the degree of receptor occupancy for the protein that transports serotonin. For example, 80% occupancy of striatal receptors is associated with a good therapeutic effect after 4 weeks of treatment with SSRIs. In the case of citalopram, a concentration of at least 50 ng/mL is required to obtain 80% striatal receptor occupancy.
With this type of study, it has been possible to identify a therapeutic range for each drug, below which the concentration of the molecule is considered insufficient to determine a satisfactory clinical response, while on the other hand in cases where the concentration exceeds the upper limit, the emergence of side effects is very likely.

Prediction of antidepressant response can be improved by a combination of early response assessment and plasma drug monitoring: in a multicenter open-label study on citalopram prescribed to 55 patients admitted with a diagnosis of major depression of moderate to severe severity [45], it was demonstrated that by using early response assessment to drug treatment, as measured on the HAM-D Scale (using a score of 24 as cut-off point) with plasma concentrations measured at day 7 (using a value of > 35 ng/ml as a cut off point), it was possible to predict antidepressant response at day 35 with a positive predictive value of 67% and a negative predictive value of 88%. A more recent similar study [46], assessed treatment with venlafaxine in a group of 88 patients and demonstrated that the predictive ability is even more reliable if plasma concentration measurements of the active metabolite (O-desmethyl-venlafaxine) are also considered.
In conclusion, there is sufficient evidence to show that the effect of action of antidepressants can be observed as early as 7-10 days of treatment. Therefore, onset of clinical response to antidepressant treatment is no longer just a matter of patience and can be influenced by prescribing practices. It becomes more challenging to identify effective treatment strategies when there is no response to treatment for which methodologically different research is needed. However, current reliable data and empirical experience have allowed clinicians to formulate valid treatment algorithms.
Finally, further understanding and research on the latency of action of antipsychotic drugs is also warranted [47].

Take home messages for psychiatric care

- The therapeutic effect of antidepressants is generally thought to take several weeks
- Several recent studies have however found evidence of an early treatment response, occurring within the first 2 weeks of antidepressant treatment
- Early treatment response, in association with Therapeutic Drug Monitoring, may predict treatment outcome

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