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DO WE NEED NEW THERAPEUTIC STRATEGIES FOR DEPRESSION?

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INTRODUCTION

Depression is a frequent, recurrent and chronic condition with high levels of functional disability (Mueller et al. 1999, Kessler et al. 2003, Posternak 2006.). Depression is also associated with excess all-cause mortality (reviewed in: Lépine and Briley 2011). Despite of growing number of different antidepressants, still less than 50% of all patients treated with the currently available antidepressants show full remission and that treatment - resistant depression (TRD) occurs frequently in clinical practice (Crisafulli et al. 2011, Fornaro & Giosue 2010). Before starting new strategies for the treatment, we recommend to consider: clinical diagnostic and recognition of relevant features of depression; definition of an adequate treatment; definitions of TRD; our knowledge of the pathogenetic mechanisms of depression and understanding the antidepressant (AD) mechanisms of action.

CLINICAL RECOGNITION OF THE DEPRESSION, ADEQUATE TREATMENT AND TREATMENT-RESISTANT DEPRESSION

World Health Organization (WHO) estimated that 5-10% of the population at any given time is suffering from identifiable depression, while the life-time risk of developing depression is 10-20% in females and slightly less in males (WHO 2001). Depression is still under-diagnosed and under-treated (Fleck et al. 2009). Between 30 and 60% of depression cases are not detected by the general clinician (Ronalds et al. 1997, Rost et al. 1998). When depressed patients are diagnosed and treated, many of depressed patients do not receive adequate treatment. Here we can ask: what is adequate treatment? Despite sophisticated guidelines, we still don't know which antidepressant and which dosage to use as first line treatment. We don't know when to start considering the second line treatment. We also do not know which of often recommended second line strategies: the dose escalation, augmentation and switching are the better than the others.

The recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that one-third of patients reach full remission after one treatment trial, with only two-thirds reaching remission after four treatment trials (Crisafulli et al. 2011.). Approximately one-third of patients with depression appear to be treatment resistant (Nemeroff 2007). Treatment-resistant depression (TRD) is therefore a common problem in the clinical practice. Those difficult-to-treat patients have prominent suicidal ideation and hopelessness (Papakostas et al. 2003), greater number of psychiatric hospitalizations (Crown et al. 2002), use of more psychotropic medications (Crown et al. 2002) and higher medical cost (Gibson et al. 2010; Crown et al. 2002) compared to non-TRD patients.

In spite the evidences of insufficient treatment, the definition of an adequate treatment with antidepressant medication and the definitions of treatment resistance depression remains unclear.

Therefore, before starting with second and third line strategies, we should carefully evaluate clinical features and depression subtype, (such as psychotic, atypical and bipolar features), often requiring more personalized rapprochement. Our recommendation is to take appropriate patient history and evaluate co morbid conditions. We should also evaluate compliance, because poor compliance leads to the ineffective treatment.

PATHOGENETIC MECHANISMS OF DEPRESSION AND UNDERSTANDING THE AD MECHANISMS OF ACTION

Our incomplete knowledge of the pathogenetic mechanisms of depression contributes to insufficient and inadequate treatment. Antidepressant drug development efforts have focused mostly on impaired neurotransmission and were primarily aimed to improve tolerability (Marks et al. 2008.). Apart from disturbed neurotransmission, there are several different mechanisms underlying the etiology of depression. Disturbed circadian rhythms, disturbed HPA axis, chronic, low grade inflammation, risk alleles, decreased level of neuronal growth factors and disrupted neuronal circuits

also contribute to pathophysiology of depression and we don't have adequate treatment approach to those mechanisms.

However, recent advances in understanding how antidepressants act at the cellular level, suggest that dysfunctional neural connections which underlie depresssion, may be corrected by antidepressants. Era of personalized medicine based on gene profiles is expected to enable the standard antidepressants to be used more effectively, so that new types of antidepressants may not be necessary. Nevertheless, the next generation of antidepressants might target non-monoaminergic mechanisms in order to improve treatments for depression.

CONCLUSION

Since one third depressed patients are treatment-resistant, we obviously need new therapeutic strategies for depression. However, before starting next line strategies, we should carefully consider clinical features of depression, compliance and co morbidities. Today, in our clinical judgment, we should include recent knowledge about antidepressants acting at the cellular level and advances in the field of pharmacogenomics with personalized medicine treatments. Moreover, the next generation of antidepressants will probably target not only monoaminergic mechanisms of action and, along with currently available antidepressants they will offer many benefits for future therapeutic approaches.

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