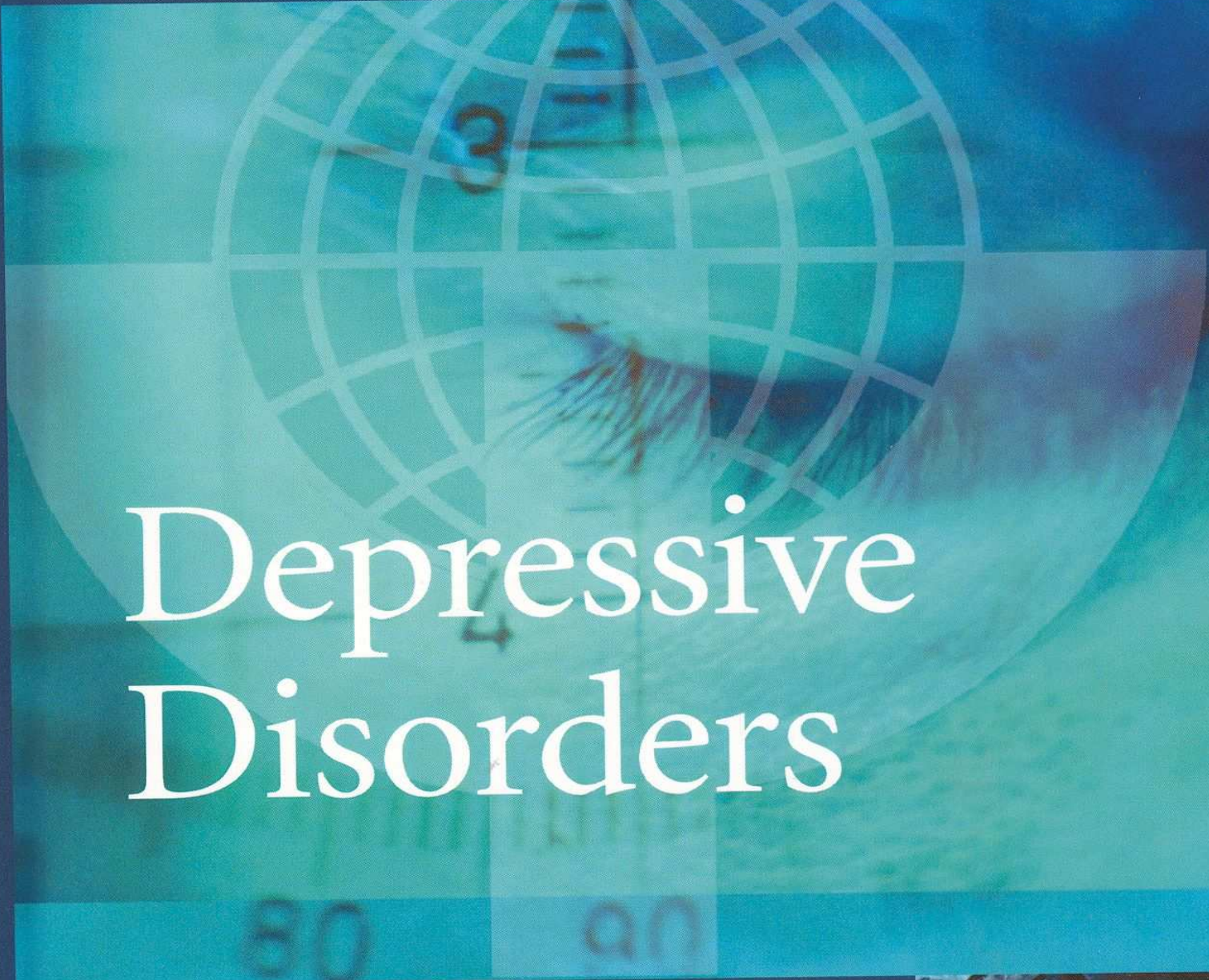


Evidence and Experience in Psychiatry



Helen Herrman, Mario Maj and Norman Sartorius



Depressive Disorders

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Challenges in Concept and Practice

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It is always difficult to overview antidepressants in a concise and practically useful way. There are four main problems.

The first is the classification. Classifying antidepressants according to the chemical structure (the number of cycles) is simple, but useless in a clinical setting. On the other hand, practical clinical criteria for the classification of antidepressant compounds are difficult to define. So, as yet, the most useful classification criterion appears to be the mode of action. Nevertheless, even this can be a source of misunderstanding because there are several different views on the clinically relevant mechanisms of antidepressant action. These mechanisms include:

- (1) monoamine re-uptake inhibition;
- (2) blockade of presynaptic inhibiting receptors (α_2);
- (3) inhibition of degrading enzymes (MAO, COMT);
- (4) increased expression of brain derived neurotrophic factor (BDNF);
- (5) antagonism of stress hormones (CRH);
- (6) antagonism on neurokinine receptors (NK_1);
- (7) synchronisation of circadian rhythms (melatonin derivatives);
- (8) inhibition of a regional brain activity in the anterior cingulate and/or facilitation of a frontal control over limbic activity;
- (9) other.

The first three of these share an increase of monoamine activity on the synaptic cleft as a common denominator (monoamine theory of depression). Another possibility – the supply with monoamine precursors like L-Trp or L-DOPA – was revealed to be quite inefficient. The fourth mechanism represents a different ‘level’ of view (the ‘molecular–cellular theory of depression’; Duman, Heninger and Nestler, 1997) and also explains mechanisms of some nonpharmacological antidepressant modalities such as ECT. The fifth mechanism is

compatible with an increased uptake of serotonin into presynaptic endings and can partially explain the paradoxical mode of action of tianeptine. The sixth mechanism represents the conceptual link between depression and (central) pain. The seventh may explain the mode of action of light therapy. The producers of agomelatine claim it may even be more important than serotonin 5HT_{2C} antagonism. The eighth mechanism can explain the promising results of deep brain stimulation (inhibition) focused on Cg25 (Mayberg *et al.*, 2005) and of rTMS and the almost miraculous reports of the effect of ketamine on treatment-resistant patients Zarate *et al.*, 2006). It is also in accordance with the predictive power of EEG cordance, where a decrease of cordance in the theta band in the frontal leads clearly predicts the treatment outcome of antidepressants (Cook *et al.*, 2002; Bares *et al.*, 2007). At the same time, this decrease of cordance seems to reflect the decrease of Cg25 activity.

The second problem is the clinical relevance in the light of the dilemma of categorical versus dimensional understanding of mental disorders. So-called antidepressants are useful to treat not only depression but also anxiety (SSRI, venlafaxine), sleep disorders, sexual disorders (mirtazapine, trazodone), smoking cessation (bupropion), pre-menstrual syndrome, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, eating disorders (SSRI) and others.

The third problem is the fuzzy demarcation among psychotropics. There are reports on the antidepressant effects of antipsychotics (olanzapine; Takahashi *et al.*, 2008), lithium (Náhunek, Švestka and Rodová, 1971), stimulants (methylphenidate; Huang *et al.*, 2008) and other drugs.

One of the prominent side-effects of antidepressive treatment is weight gain. Authors of the chapter point out weight gain after use of almost all antidepressants. On the other hand, other researchers (Wurtman and Wurtman, 1996) refer to the positive effect of serotonin (and SSRI) not only on depression but also on craving and carbohydrate consumption. They suggest particular subtypes of depression sometimes present a higher risk for obesity and diabetes than antidepressant treatment as such. In summary, weight gain may be a significant problem only in antidepressants with antihistaminic activity (mirtazapine, TCA), while administration of other antidepressants may also benefit from their serotonin-like anticraving activity.

The fourth problem concerns the efficacy of antidepressants, which has been recently challenged by Kirsh *et al.* (2008). They concluded in their meta-analysis of studies of selected antidepressants submitted to the FDA that the difference between them (fluoxetine, venlafaxine, nefazodone and paroxetine) and placebo does not reach the criterion for clinically significant effect size. This meta-analysis has been subsequently criticised (e.g. by Höschl, 2008) and the usefulness of these antidepressants demonstrated. For example, an inverse correlation between their prescription and suicide rates has been shown (Rihmer, Rihmer and Isaccson, 2005; Isaccson, 2007).

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