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New antidepressants or more of the same?

Effective antidepressant drugs have been available for half a century since the first monoamine oxidase inhibitor (MAOI), isoniazid, and the prototype tricyclic antidepressant (TCA), imipramine, were introduced into therapy (Leonard and Spencer 1990). The use of MAOIs declined when reports appeared of hypertensive crises associated with ingestion of dietary tyramine, and the TCAs, despite their shortcomings in safety and tolerability, became the mainstays of treatment. A second generation of drugs of various classes was developed with diverse chemical structures and different mechanisms of action (Pinder and Wieringa 1993), of which the most widely prescribed have been the selective serotonin reuptake inhibitors (SSRIs). Although modern drug discovery technologies like combinatorial chemistry and high-throughput screening have made less likely the identification of truly novel agents (Pinder 2001), new agents and biological targets continue to be investigated (Bosker et al 2004). Psychological treatments, including cognitive and interpersonal therapies, also have their place in the acute and maintenance treatment of depression (DeRubels et al 2005).

Two of the new kids on the block have been reviewed in recent issues of *Neuropsychiatric Disease and Treatment*. One is a new formulation of an old irreversible MAOI, selegiline, and is the first transdermal antidepressant to be introduced (Lee and Chen 2007), while the second, agomelatine, has a novel mechanism of action in being a melatonin receptor agonist and a serotonergic (5-HT_{2c}) antagonist (Kennedy and Eisfeld 2007). The selegiline transdermal system (STS) has already received US Food and Drug Administration (FDA)-approval, while agomelatine may be approved shortly by the European Agency for the Evaluation of Medicinal Products (EMEA). Do these newcomers represent major advances in therapy?

For US physicians, the use of MAOIs has long been restricted to phenelzine, tranylcypromine, and isocarboxazid, with most prescriptions being written for phenelzine. As the only MAOI available in the USA for the treatment of depression that does not require dietary restriction at clinically effective doses, STS is likely to find a place in the antidepressant armamentarium particularly for the treatment of atypical depression, treatment-resistant patients, and those with accompanying anxiety disorders (Lee and Chen 2007). Outside the USA, physicians have long had access to the reversible MAOI moclobemide which also lacks dietary restrictions. If STS comes to Europe or to other parts of the world, it is likely to be the novelty factor that prompts physicians to prescribe a transdermal agent or the demand from patients for a non-oral therapy, rather than any perceived superiority to moclobemide. Oral selegiline is approved only as an adjunctive treatment in Parkinson's disease; it enjoyed a brief vogue as a neuroprotective agent in monotherapy, but large clinical trials showed that it was more suitable as an add-on to dopamine agonists particularly levodopa.

Agomelatine is the more interesting newcomer from the mechanistic viewpoint. As a modulator of both the M_1 and M_2 types of melatonin receptor, it could play a role in regulating the suprachiasmatic nucleus circadian clock and thereby restore disruption of the sleep-wake cycle and circadian rhythms. Depression is characterized in part by altered patterns of sleep, and both sleep- and REM-sleep deprivation are effective as acute treatments. The antidepressant efficacy and relative safety of agomelatine have been established in several large clinical trials while its sleep restorative properties,

lack of sedation and minimal effects on sexual function make it suitable for general use (Kennedy and Eisfeld 2007). Its potential role in sleep disorders and jet lag have hardly been explored so far.

Neither of these drugs represents a breakthrough in the treatment of depression, but are the latest incremental advances in our ability to address the most common mental health problem of our age. We still need antidepressants that act faster to produce more response and remission; the gains of the last decades since the introduction of MAOIs and TCAs have been more in safety and tolerability than in efficacy. Improvements in diagnosis and our emerging ability to characterize different forms of depression in biological terms may ultimately help to develop more targeted treatments of greater efficacy.

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