

The well of novel antidepressants: running dry

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Until last year, the last decade had not seen the introduction of novel antidepressant medications. The melatonin agonist/serotonin (5-HT)_{2C} antagonist agomelatine was the one exception.¹ The antidepressants that reached the market earlier were produced in the early 1990s and subsequently redeveloped. The nontricyclic dual serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine was initially tested at subtherapeutic doses (5–20 mg/d)² and then at effective doses (60–120 mg/d).³ Once the technology was available, the stereoisomer S-citalopram, whose inhibition of 5-HT reuptake is dampened by the R-stereoisomer in racemic citalopram, was produced.⁴ Desvenlafaxine is the main metabolite of venlafaxine that is eliminated unmetabolized by the kidney and that appears to carry the antidepressant effect of its parent compound, venlafaxine.⁵ There are several reasons why this field has been in a relative drought.

The first problem that arose in the early 1990s was the eagerness of industry to get their candidate antidepressants quickly to the market at the expense of performing solid pivotal trials. For example, a very large double-blind trial was carried out with the selective noradrenergic reuptake inhibitor (NRI) tomoxetine (later redeveloped as atomoxetine for its use in attention deficit disorder) in a 3-arm study. It was tested along with a placebo and a desipramine group. The trial was a failed trial in the sense that neither the active control desipramine nor tomoxetine separated from placebo. In contrast, the trial would have been declared negative had the NRI desipramine separated from placebo and tomoxetine had not. The development of tomoxetine was discontinued. Yet the nontricyclic NRI reboxetine is on the market in many countries worldwide.⁶

A second problem that persists in this field is the inadequate dosing of the candidate compounds in clinical trials. Duloxetine was initially tested at insufficient doses even to obtain a threshold inhibition of 5-HT reuptake. This was subsequently demonstrated in humans using a paradigm that had been available for decades — 5-HT depletion in whole blood by reuptake inhibition.⁷ This was confirmed much later with the availability of positron emission tomography ligands

for the 5-HT transporter in humans. We now know that all antidepressants that block, at a minimum, 5-HT reuptake must achieve a sustained threshold of 80% occupancy to exert an antidepressant action.⁸ Duloxetine attains this level of occupancy at 40 mg/d but not in a sustained manner. The currently recommended dose of 60 mg/d meets this level of occupancy in a sustained manner.⁹ With the technology available now, such errors should not be made.

A third problem stemmed from the enthusiasm about the possibility of searching the genome for new targets in the 1990s. Indeed, many opinion leaders were pushing the view that no significant progress had been made since the discovery of the antidepressant effect of tricyclics and monoamine oxidase inhibitors in the 1950s. These drugs act primarily by enhancing monoamines and subsequent refinements of these agents (e.g., in the form of SSRIs) were not considered to be important advancements. Novel agents were nevertheless developed, such as the catecholamine releaser bupropion,¹⁰ the potent noradrenergic and dopaminergic reuptake inhibitor nomifensine¹¹ and the α_2 -adrenoceptor antagonist mirtazapine.¹² Yet these compounds still appear to exert their therapeutic action in unipolar depression by increasing monoaminergic transmission.

Searching for entirely novel targets in the 1990s was certainly indicated then, and is to this day as well, but not at the expense of neglecting the monoaminergic trail. What if we had it right from the beginning? What if the road to an acute antidepressant effect largely depends, in most patients, on an enhancement of the function of one or more monoaminergic systems? Following the discovery of penicillin, the field seemed to believe that the principle was right from the beginning and never looked back. With regards to antidepressants, there were already multimonoaminergic target drugs being developed in the early 1990s, agents, for example, that would act at the 5-HT transporter, block 5-HT₂ receptors and activate 5-HT_{1A} receptors.¹³ Some of these agents were tested in the clinic, but at a time when the unmanaged placebo response was already posing a threat to reliable clinical testing of antidepressants. Such agents are now again a “new” trend.¹⁴

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A fourth problem is the limited period industry has to sell their medications under patent protection. On one hand, industry has to be kept in check to ensure that their novel medications are not sold at exorbitant prices; on the other hand, enough profits have to be generated to ensure that their pipelines are not depleted. The patent laws were likely adequate when they were introduced. However, the horizon has dramatically changed since. The cost to bring an antidepressant to market has been increasing exponentially. In addition, once on the market, medications sometimes have to be withdrawn because of unexpected adverse events after they have become "blockbusters," such as nomifensine (Merital).¹⁵ On some occasions, antidepressants may become contraindicated for the wrong reasons, as in the case of hormone replacement therapy, especially when it was wrongly used in women in their sixties with deleterious effects.¹⁶

A fifth problem is the financial drain exerted by generic medications on the original brands. Generic companies routinely challenge patent laws of brand medications, obviously not before major marketing campaigns have been undertaken to make a medication a success. They sometimes win their claims, as was the case recently in Canada for olanzapine. This draws large sums of money away from research and development, a department that is nonexistent at generic companies. Most generics for relatively new medications in Canada are then sold at 75%–80% of the cost of the original brand. Moreover, their quality can sometimes be suboptimal. For instance, when we assessed the maximum concentration (C_{max}) of Novo-venlafaxine XR and Gen-citalopram, the plasma levels of the generic citalopram were identical to those of Celexa, but the C_{max} of the generic venlafaxine was 51% higher than that of Effexor XR.¹⁷ The accepted norm for this parameter in the United States and Europe is 80% to 125%.

Some, if not all, of these problems have recently led 2 large pharmaceutical firms to pull away from antidepressant drug research. Having fewer players in the field is certainly going to limit the number of candidates lining up for clinical testing. It is hoped that the ingenuity of our scientific community will be able to devise novel medications and bring them to use in our patients through capital ventures. It is ironic that in an era when depression carries the largest burden of all diseases (measured in disability-adjusted life years) in middle- to high-income countries, the efforts to identify novel antidepressants are diminishing. The World Health Organization (WHO) estimates that by the year 2030 the burden of unipolar depression will be first worldwide, still ahead of ischemic heart disease.¹⁸ With no control of the obesity epidemic in the foreseeable future, the burden of ischemic heart disease is anticipated to increase by 30%, whereas that of unipolar depression will grow by 50% by 2030 according to WHO estimates.¹⁸ Our standards of care have to change, but, above all, the well of novel antidepressants has to be replenished.

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References

- Kennedy SH. Agomelatine: efficacy at each phase of antidepressant treatment. *CNS Drugs* 2009;23(Suppl 2):41-7.
- Joubert AF, du Plessis AD, Farles D, et al. High placebo response rate versus clinical impression with the new antidepressant duloxetine. *Biol Psychiatry* 1997;42(Suppl 1):229S.
- Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 2002;36:106-32.
- Sánchez C, Bøgesø KP, Ebert B, et al. Escitalopram versus citalopram: the surprising role of the R-enantiomer. *Psychopharmacology (Berl)* 2004;174:163-76.
- Lobello KW, Preskorn SH, Guico-Pabia CJ, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. *J Clin Psychiatry* 2010 Apr. 6 [Epub ahead of print].
- Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. *Ann Pharmacother* 2000;34:1302-12.
- Turcotte JE, Debonnel G, de Montigny C, et al. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacology* 2001;24:511-21.
- Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry* 2004;161:826-35.
- Takano A, Suzuki K, Kosaka J, et al. A dose-finding study of duloxetine based on serotonin transporter occupancy. *Psychopharmacology (Berl)* 2006;185:395-9.
- El Mansari M, Ghanbari R, Janssen S, et al. Sustained administration of bupropion alters the neuronal activity of serotonin, norepinephrine but not dopamine neurons in the rat brain. *Neuropharmacology* 2008;55:1191-8.
- Katz NS, Guiard BP, El Mansari M, et al. Effects of acute and sustained administration of the catecholamine reuptake inhibitor nomifensine on the firing activity of monoaminergic neurons. *J Psychopharmacol* 2009 Nov. 25 [Epub ahead of print].
- Tremblay P, Blier P. Catecholaminergic strategies for the treatment of major depression. *Curr Drug Targets* 2006;7:149-58.
- Shah VR, Srinivas NR, Campbell DA, et al. High-performance liquid chromatographic-ultraviolet assay for the simultaneous quantitation of BMS-181101 and its putative hydroxy metabolites in rat and monkey plasma. *Biomed Chromatogr* 1996;10:135-8.
- Artigas F, Dragheim M, Loft H, et al. A randomized, double-blind, placebo-controlled, active-reference study of Lu AA21004 in patients with major depression. *Eur Neuropsychopharmacol* 2009; 19(Suppl 3):S426-7.
- Kinney JL. Nomifensine maleate: a new second-generation antidepressant. *Clin Pharm* 1985;4:625-36.
- Vickers MR, MacLennan AH, Lawton B, et al. Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women. *BMJ* 2007;335:239.
- Chenu F, Batten LA, Zernig G, et al. Comparison of pharmacokinetic profiles of brand-name and generic formulations of citalopram and venlafaxine: a crossover study. *J Clin Psychiatry* 2009;70:958-66.
- World Health Organization (WHO). Burden of disease: DALY. In: *The global burden of disease: 2004 update*. Geneva (Switzerland): WHO; Available: www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part4.pdf (accessed 2010 June 1).