

- Essential PsychopharmaStahlogy -

Strategies for Innovating New Treatments in Psychiatry

Are active enantiomers, controlled-release technologies, and active metabolites gimmicks or incremental advances?

Most innovation in psychiatry is evolutionary rather than revolutionary.

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Commercial success versus true innovation: can these be aligned?

Drug development has come under fire lately for being dominated by patent extension maneuvers designed to keep drug prices high without notable innovation (see poll on page 1). Although this can happen, such maneuvers

but some still question how much of an innovation this represents. Probably the most clever use of enantiomers is to take a product never developed in the United States as the racemate and develop its active enantiomer while simultaneously earning a novel claim. That example is eszopiclone, the first agent

Depakote ER). Others, however, may not add much value to the original compound and are not yet commercially successful (e.g., Paxil CR, Xanax XR, Prozac weekly, Ambien CR). Being able to skip a lunchtime dosing of a stimulant is not a trivial innovation, as this reduces the need to distribute controlled substances at school,

enhances compliance by eliminating a dose, and much reduces the stigma of taking a medication at school around peers. Thus, the controlled-release stimulants have enjoyed commercial success.

Drugs, prodrugs, and active metabolites

Finally, active metabolites may or may not eventually prove to be innovations or commercial successes. Three examples currently in clinical development are listed in Table 3.³

Whereas it may be difficult to see the added value of desmethylvenlafaxine over venlafaxine, radafaxine may have greater potency for the noradrenergic transporter over bupropion, and the oxcarbazepine metabolite licarbazepine may give the chance to develop this compound for bipolar disorder when the parent compound was not exploited for this purpose.

The bottom line—Most clinical innovation in therapeutics for psychiatry comes after initial marketing of compounds for different indications. To get the most out of a compound's commercial potential as well as its therapeutic potential, the strategy is to “find what you are not looking for,”³ namely by discovering unforeseen and unpredicted therapeutic applications of compounds in psychiatry.

TAKE-HOME POINTS

1. New drug development can proceed by many pathways. Although breakthroughs can occur due to new compounds acting with novel mechanisms of action, most advances are more incremental.
2. A favored strategy is to find new uses for products developed for a different indication

Table 1: Gimmicks or incremental innovations? Effective and ineffective uses of active enantiomers

ORIGINAL DRUG	STRATEGY	COMMENT
citalopram	active enantiomer (escitalopram)	-commercially successful -? innovation
zopiclone	active enantiomer (eszopiclone)	-patent expiry of racemate -novel claim for chronic insomnia
modafinil	active enantiomer (armodafinil)	-longer half-life -? innovation
methylphenidate	methylphenidate active enantiomer (dexmethylphenidate)	-? innovation

are rarely commercially successful unless they also provide a new advantage to the old compound. We all wish for breakthrough compounds to treat new disorders with a novel mechanism of action, but the truth is that most innovation in psychiatry is evolutionary rather than revolutionary.¹⁻³ We often learn about the potential of an old drug for a new indication late in the patent life, and although this creates the possibility of fulfilling an unmet therapeutic need, there may be no commercial incentive to pursue this need. However, it may be possible to use three strategies to provide a commercial incentive and, when matched with fulfilling unmet therapeutic needs, lead to incremental advances in psychopharmacology.

Mirror, mirror on the wall, which enantiomer is fairest of them all?

Active enantiomers can provide one such strategy to commercialize novel psychiatric indications of older drugs (Table 1).³⁻⁴ Probably the most successful commercial example of this is the active enantiomer of citalopram (escitalpram). It may provide more selectivity of action and better tolerability,

approved without short-term dosing limits for insomnia.^{5,6}

At long last, long-lasting psychotropic drugs

Extended-release formulations have frequently been debated as incremental innovations or patent extension gimmicks (see poll on page 1).⁷ They can be both (Table 2).³ Perhaps the most innovative use of extended-release technology is the transdermal delivery of selegiline to add major depression as a claim to a drug approved in the oral dosage form for Parkinson's disease. Transdermal delivery increases bioavailability of selegiline to the brain, resulting in robust MAO A and MAO B inhibition. This action predicts high efficacy for major depression. At the same time, transdermal delivery of selegiline bypasses the gut and reduces MAO A inhibition there, predicting less need for dietary restriction of tyramine and fewer drug interactions.

Some extended-release technologies convert short-acting drugs to once-a-day administration while often improving tolerability and are commercial successes (Table 2; e.g., Effexor XR, controlled-release stimulants, Wellbutrin XL,

Table 2: Gimmicks or incremental innovations? Effective and ineffective uses of extended-release

ORIGINAL DRUG	STRATEGY	COMMENT
selegiline	transdermal delivery	-promises to convert an oral drug for Parkinson's disease into a once-a-day antidepressant with high efficacy and reduced dietary restrictions (in development)
methylphenidate	active enantiomer (dexamethylphenidate) with extended-release	-? innovation
paroxetine	extended-release (Paxil CR)	-? innovation -not commercially successful
bupropion	extended-release (Wellbutrin XL)	-converting from twice daily to once daily considered a real improvement -commercially successful
venlafaxine	extended-release (Effexor XR)	-once daily and reduced nausea -commercially successful
fluoxetine	extended-release (Prozac weekly)	-? innovation -not commercially successful
divalproex	extended-release (Depakote ER)	-once daily -fewer peak dose side effects -commercially successful
alprazolam	extended-release (Xanax XR)	-? innovation -once or twice daily -not commercially successful
risperidone	biweekly depot injection (Risperdal Consta)	-useful for compliance -limited commercial success
zolpidem	extended-release (Ambien CR)	-? innovation
indiplon	modified-release (indiplon MR)	-immediate release for short duration effects when desired (in development) -modified-release to extend duration and could improve efficacy (in development)
zaleplon	extended-release	-could improve efficacy (in development)
methylphenidate	transdermal patch	-? innovation (in development)
stimulants d and l amphetamine salts methylphenidate	extended-release Adderall XR Concerta; Ritalin LA Metadate CD	-eliminated need for lunchtime dosing -commercially successful
lamotrigine	once daily extended-release	-? innovation
memantine	once daily extended-release	-? innovation

(e.g. atypical antipsychotics for bipolar disorder), which works well if there is sufficient patent life remaining on the drug to provide a commercial incentive to further develop the drug.

- When a new use is discovered after the original patent has expired, it is still possible to provide commercial incentive for further development, not only by changes in the law (e.g. use patents, patent restoration, Waxman-Hatch extension), but also by several scientific strategies: active enantiomers, controlled-release technologies, and active metabolites.
- Sometimes these approaches have tried to extend patent life without adding any notable advantage and usually are not commercially successful.
- At their best, patent extension strategies can provide a commercial incentive to prove the safety and efficacy of old drugs for new indications. ♣

Table 3: Gimmicks or incremental innovations? Effective and ineffective uses of active metabolites

ORIGINAL DRUG	STRATEGY	COMMENT
venlafaxine	-active metabolite -desmethylvenlafaxine	-? innovation
bupropion	-active enantiomer of active metabolite +6-hydroxybupropion or radafaxine	-enhanced noradrenergic action compared to bupropion
oxcarbazepine	-active enantiomer of active metabolite -monohydroxy derivative -S-licarbazepine	-chance to develop for bipolar disorder

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