Newer Antidepressants in the Primary Care Setting

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Because major depression has negative effects on other disease states, proper recognition and treatment of depression are important in the primary care setting. Although the perfect antidepressant does not yet exist, newer antidepressants have advanced the field. This article will summarize key features of 3 newer antidepressants that represent advances in psychopharmacology: mirtazapine, which has a dual effect on serotonergic and noradrenergic systems; escitalopram, the latest selective serotonin reuptake inhibitor, which is the first pure antidepressant stereoisomer in clinical use; and duloxetine, a dual reuptake inhibitor of norepinephrine and serotonin that is expected to be clinically available in the near future. *(Prim Care Companion J Clin Psychiatry 2004;6[suppl 1]:3–6)*

Major depression continues to be an underrecognized entity in primary care settings and a source of ever-increasing disability compared with other diseases. Not only is depression itself debilitating, but it also has additive negative effects on other significant disease states, notably coronary artery disease and acute myocardial infarction, where depressive comorbidity clearly increases mortality. Therefore, proper recognition and treatment of depression are important in the primary care setting.

The perfect antidepressant does not yet exist. In fact, development of an agent that possesses all of the characteristics that clinicians might desire may not be practically possible. Rapid onset of action, high remission rates in broad populations of patients, plus tolerability comparable with placebo are some of the key features of the ideal antidepressant. In spite of their limitations, newer antidepressants have advanced the field, sometimes in novel fashion. This article will summarize key features of 3 newer antidepressants that represent advances in psychopharmacology. Mirtazapine is included in this discussion even though it has been available for a number of years. Its significant antidepressant effects without reuptake inhibition of monoamine neurotransmitters, its dual effect on serotonergic and noradrenergic systems, and its high remission rates in controlled trials may be less familiar to and less appreciated by many primary care practitioners. Escitalopram, the latest in a long line of selective serotonin reuptake inhibitors (SSRIs), is the first pure antidepressant stereoisomer in clinical use and is worthy of attention in that respect. Duloxetine, a dual reuptake inhibitor of norepinephrine and serotonin, is expected to be clinically available in the near future.

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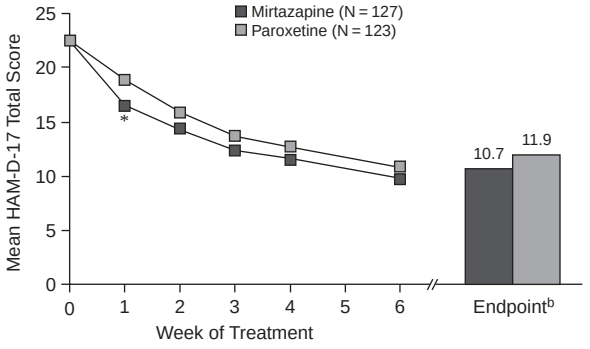
MIRTAZAPINE

Mirtazapine enhances both serotonergic and noradrenergic neurotransmission, but not by inhibiting the reuptake of these neurotransmitters. It has specific serotonergic effects mediated through the blockade of postsynaptic 5-HT_2 and 5-HT_3 receptors. This blockade leads to enhancements in 5-HT_{1A}–mediated neurotransmission. Mirtazapine antagonizes α_2-heteroreceptors, further enhancing 5-HT_{1A} effects, while antagonism at α_2-autoreceptors is responsible for noradrenergic effects.[1]

Controlled clinical trials have demonstrated the superior efficacy of mirtazapine over placebo[2] and trazodone,[3] comparable efficacy to the tricyclic antidepressants (TCAs) amitriptyline[2] and doxepin,[4] and faster onset of action than the SSRIs citalopram[5] and paroxetine[6,7] (Figure 1). A 2-year comparison of mirtazapine and amitriptyline[8] showed comparable efficacy at 20 weeks but superiority of mirtazapine over amitriptyline at the study endpoint. Having remission rates comparable to those of the TCAs is important, since safety advantages gained over the last decade through the increased use of SSRIs may have been offset by a reduction in depression remission rates—the gold standard of any therapeutic intervention. Additionally, a post hoc analysis of head-to-head trials with SSRIs by Quitkin et al.[9] suggested a more rapid response rate with mirtazapine (Table 1), although this analysis lacked a placebo group and a prospective methodology. Evidence also suggests mirtazapine efficacy in those with severe depression studied as inpatients,[10] in those who failed SSRI

Figure 1. Change in Mean 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Total Score During Treatment (intent-to-treat sample)[a]



[a]Reprinted with permission from Benkert et al.[6] Observed case analysis for weeks 1 to 6 assessments: number of patients (mirtazapine/paroxetine) = 125/123, 121/114, 117/111, 115/110, and 109/104 at weeks 1, 2, 3, 4, and 6, respectively. Mean daily dose was 32.7 mg for mirtazapine and 22.9 mg for paroxetine.
[b]Last-observation-carried-forward analysis for endpoint.
*p ≤ .01, mirtazapine vs. paroxetine (2-sided t test).

Table 1. Persistent and Nonpersistent Responders for Mirtazapine vs. Fluoxetine, Paroxetine, and Citalopram Groups[a]

	Proportion of Patients (%)			
Status	Mirtazapine (N = 298)	Fluoxetine (N = 46)	Paroxetine (N = 110)	Citalopram (N = 129)
Persistent responders				
Week 1	13	9	6	5
Week 2	20	20	25	20
Week 3	15	15	14	28
Week 4	10	9	9	15
Week 6	9	7	9	12
Nonpersistent responders[b]	7	13	8	5
Nonpersistent nonresponders[c]	9	9	4	4
Never improved	15	20	25	10
Total responders	75	72	71	86
	Mirtazapine	SSRIs		
Week 1 responders	38	18	} $\chi^2 = 6.95$, df = 1, p = .008	
All others	260	267		

[a]Reprinted with permission from Quitkin et al.[9] Response determined by Clinical Global Impressions-Improvement scale score.
[b]Responded, relapsed, rated responder at week 6.
[c]Responded, relapsed, not rated responder at week 6.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

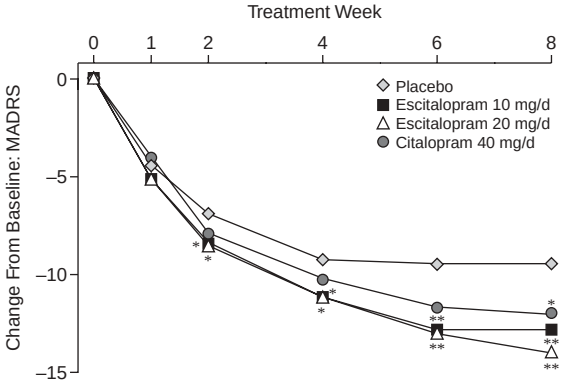
trials,[11] and in those who had remitted but were at high risk for relapse.[12] Mirtazapine significantly improved symptoms of anxiety in depressed patients studied in clinical trials.[5–7]

Sedation and weight gain are the most notable side effects of mirtazapine. In a study of geriatric depression,[7] mirtazapine's tolerability was significantly better than that of paroxetine. In head-to-head controlled comparisons of mirtazapine with citalopram[5] and paroxetine,[6] dropouts due to adverse events were not statistically different. In the 8-week comparison of venlafaxine to mirtazapine in hospitalized patients,[10] significantly more patients in the venlafaxine group dropped out due to adverse events, probably due to the rapid escalation in doses of both medications.

ESCITALOPRAM

Escitalopram is the *S*-isomer of citalopram. It is a very specific serotonin reuptake inhibitor, the development of which attempts to clinically utilize the most therapeutically active stereoisomer of citalopram. The goal is to reduce troublesome side effects of the stereoisomer combination while maximizing clinical effect to yield gains in efficacy and tolerability. Escitalopram has approximately 30 times the affinity to human serotonin transporters of *R*-citalopram in vitro,[13] suggesting that the *S*-isomer is the more clinically active of the two.[14] In vivo microdialysis studies of rat brain cortex also show a greater propensity for escitalopram to elevate serotonin levels than for citalopram.[15] Escitalopram has little affinity for adrenergic (α_1), muscarinic (M_1), or histaminic (H_1) receptors, yielding low rates of sedation, dry mouth, and vascular side effects.

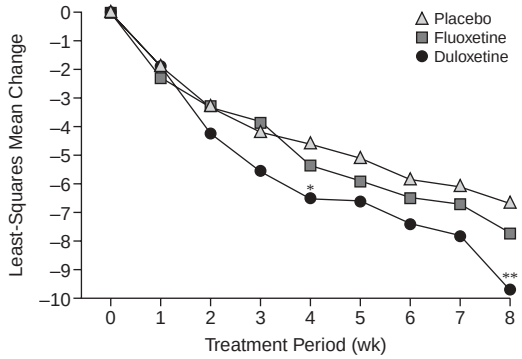
Figure 2. Mean Change From Baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) in Depressed Patients Treated With Escitalopram (10 or 20 mg/day), Citalopram, or Placebo[a]



[a]Reprinted with permission from Burke et al.[17] Patients had a minimum baseline score of 22 on the MADRS.
*p ≤ .05, compared with placebo.
**p < .01, compared with placebo.

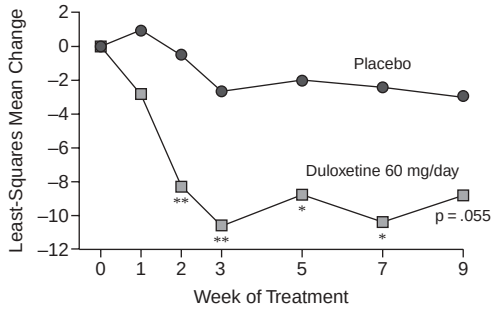
Controlled clinical trials of escitalopram in depressed outpatients have established its efficacy in depression (Figure 2); significantly, escitalopram has evidence of efficacy in a primary care study.[16,17] Reports of higher-than-anticipated remission rates (compared with other SSRIs) should be mitigated by the fact that the definition of remission used in the controlled trials of escitalopram was a Montgomery-Asberg Depression Rating Scale (MADRS) score of less than or equal to 12; the true measure of remis-

Figure 3. Effect of Placebo (N = 68), Duloxetine (N = 66), and Fluoxetine (N = 33) on 17-item Hamilton Rating Scale for Depression Total Scores (least-squares mean change from baseline) During the 8-Week Treatment[a]



[a]Reprinted with permission from Goldstein et al.[23] Duloxetine differed significantly from placebo at week 4 (*p = .049) and week 8 (**p = .009).

Figure 4. Effect of Placebo and Duloxetine 60 mg/day on Visual Analog Scale Measure of Overall Pain Severity[a]



[a]Reprinted with permission from Detke et al.[25]
*p < .05.
**p < .01.

sion using the MADRS scale is arguably a score of 10 or less. A controlled trial[18] found no significant differences in efficacy between escitalopram 10 mg/day or 20 mg/day and citalopram 40 mg/day. However, a meta-analysis[19] of 3 randomized trials of patients treated with 10 to 20 mg/day of escitalopram compared with those treated with 20 to 40 mg/day of citalopram suggested significantly greater improvements in those treated with escitalopram over the citalopram-treated group. Escitalopram effectively reduced anxious symptoms in depressed patients[17] and may have positive clinical effects in social anxiety[20] and panic disorder.[21]

Escitalopram was well tolerated in controlled trials,[16,17] with drop-out rates comparable to those treated with placebo. Mild and transient nausea was more often seen in those treated with escitalopram.[16]

DULOXETINE

Duloxetine, a dual reuptake inhibitor of synaptic serotonin and norepinephrine, is expected to become available in the near future. Duloxetine possesses roughly equivalent affinities for both human serotonin and norepinephrine transporters[22] while retaining low affinities for β_1-adrenergic, muscarinic, and histaminic receptors. In contrast to other dual reuptake inhibitor antidepressants, duloxetine appears to exert clinically demonstrable effects on both noradrenergic and serotonergic neurotransmission at starting doses. This suggests the combination of the higher remission rates associated with dual activity antidepressants without the requirement of upward dose titration necessary with TCAs, mirtazapine, and venlafaxine.

The efficacy of duloxetine for depression has been established in controlled trials using 40 to 120 mg/day given b.i.d. (Figure 3)[23] and 60 mg in a single daily dose.[24,25] The estimated probability of remission after acute treatment with duloxetine has been stated as from 43% to 56%.[23–25] When duloxetine becomes clinically available, it appears that 60 mg once daily will be indicated as both the starting and effective dose. With 60 mg given once daily, clinical effect was noted as early as week 1 on Hamilton Rating Scale for Depression (HAM-D) item 1 (depressed mood) and in clinician and patient global assessments (data on file, Eli Lilly and Company, Indianapolis, Ind.). At week 2, HAM-D scores separated from placebo and continued to increase in significance to the end of the trial. Anxiety scores also showed significant improvement over placebo.[23]

Duloxetine was well tolerated in clinical trials. Nausea, dry mouth, and constipation were the most frequently seen side effects.[24,25] Nausea was generally mild to moderate and subsided after the first week of therapy.[25] Discontinuation due to adverse events was not statistically significant between the duloxetine and placebo groups.[23] No clinically meaningful effects on blood pressure were detected.[23,25] Abrupt discontinuation was associated with transient dizziness in approximately 11% of patients.[25] The incidence of sexual dysfunction was closely monitored using the Arizona Sexual Experience Scale (ASEX). Duloxetine was associated with a low incidence of treatment-emergent sexual dysfunction not different from placebo from baseline to endpoint on the solicited ASEX total scores.[23]

Pain is a symptom often associated with depression and commonly listed as a chief complaint in depressed patients in primary care. Antidepressants have long been used to treat chronic pain states. Research suggests that antidepressants with a dual serotonin and norepinephrine effect are more effective for pain than those with single monoamine activity.[26] This fact, combined with the growing understanding that descending noradrenergic and serotonergic spinal pathways are important modulators of afferent pain fibers ascending through the spinal cord,[27] led to a focus on

painful symptoms associated with depression in the duloxetine trials. Significant reductions in overall pain severity (Figure 4), back pain, shoulder pain, time in pain while awake, and pain interfering with daily activities as measured by a visual analogue scale were observed, compared with placebo.[25]

FUTURE DIRECTIONS

No single neurotransmitter or system is responsible for the development of major depression. Now and for the foreseeable future, antidepressants will attempt to treat depression through monoaminergic effects. However, the future of antidepressant therapy includes agents that antagonize corticotrophin-releasing factor and those that act as antiglucocorticoids, agents influencing the activity of glutamate, and those that block the activity of substance P on its receptor neurokinin 1R (NK 1R).

CONCLUSION

There is no perfect antidepressant at this time, but newer antidepressants offer advantages in safety, tolerability, and efficacy. There is a growing body of evidence that antidepressants with mechanisms of action involving 2 or more monoamine systems may offer improvements in overall remission rates, time to clinical response, and efficacy in various chronic pain states. Future antidepressants will expand beyond direct effects on monoamine systems to treat depression through different pathways and, hopefully, deliver significant advances in clinical utility.

Drug names: amitriptyline (Endep, Elavil, and others), citalopram (Celexa), doxepin (Sinequan, Zonolon, and others), escitalopram (Lexapro), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Baldwin DS. Monoamine systems in depression: towards better understanding of the disorder and improved treatment options. Hum Psychopharmacol 1998;13:293–295
2. Kasper S. Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. Int Clin Psychopharmacol 1995;10:25–35
3. van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind multicentre trial in hospitalized depressed patients. Int Clin Psychopharmacol 1995;10:3–9
4. Marttila M, Jaaskelainen J, Jarvi R, et al. A double-blind study comparing the efficacy and tolerability of mirtazapine and doxepin in patients with major depression. Eur Neuropsychopharmacol 1995;5:441–446
5. Leinonen E, Skarstein J, Behnke K, et al. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Int Clin Psychopharmacol 1999;14:329–337
6. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry 2000;61:656–663
7. Schatzberg AF, Kremer C, Rodrigues HE, et al. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. Am J Geriatr Psychiatry 2002;10:541–550
8. Montgomery SA, Reimitz PE, Zivkov M. Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind, placebo-controlled study. Int Clin Psychopharmacol 1998;13:63–73
9. Quitkin FM, Taylor BP, Kremer C. Does mirtazapine have a more rapid onset than SSRIs? J Clin Psychiatry 2001;62:358–361
10. Guelfi JD, Anssear M, Timmerman L, et al. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 2001;21:425–431
11. Fava M, Dunner DL, Greist JH, et al. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry 2001;62:413–420
12. Thase ME, Nierenberg AA, Keller MB, et al. Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients. J Clin Psychiatry 2001;62:782–788
13. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–350
14. Sanchez C, Hogg S. The antidepressant effect of citalopram resides in the S-enantiomer (Lu 26-054). Biol Psychiatry 2000;47
15. Hyttel J, Bogeso KP, Perregaard J, et al. The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm Gen Sect 1992;88:157–160
16. Wade A, Lemming MO, Hedegaard BK. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002;17:95–102
17. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63:331–336
18. Gorman JM. Comparison of efficacy in placebo-controlled trials of escitalopram and citalopram [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
19. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectr 2002;7(suppl 1):40–44
20. Kasper S, Loft H, Smith RJ. Escitalopram is efficacious and well tolerated in the treatment of social anxiety disorder. Presented at the 23rd Congress of the Collegium Internationale NeuroPsychopharmacologicum; June 23–27, 2002; Montreal, Canada
21. Stahl S, Gegel I, Li D. Escitalopram in the treatment of panic disorder. Presented at the 23rd Congress of the Collegium Internationale NeuroPsychopharmacologicum; June 23–27, 2002; Montreal, Canada
22. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes and other neuronal receptors. Neuropsychopharmacology 2001;25:871–880
23. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind, placebo-controlled trial. J Clin Psychiatry 2002;63:225–231
24. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36:383–390
25. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63:308–315
26. Lynch M. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30–36
27. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Ann Rev Neurosci 1984;7: 309–338