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REVIEW

Getting the balance right: Established and emerging therapies for major depressive disorders

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Abstract: Major depressive disorder (MDD) is a common and serious illness of our times, associated with monoamine deficiency in the brain. Moreover, increased levels of cortisol, possibly caused by stress, may be related to depression. In the treatment of MDD, the use of older antidepressants such as monoamine oxidase inhibitors and tricyclic antidepressants is decreasing rapidly, mainly due to their adverse effect profiles. In contrast, the use of serotonin reuptake inhibitors and newer antidepressants, which have dual modes of action such as inhibition of the serotonin and noradrenaline or dopamine reuptake, is increasing. Novel antidepressants have additive modes of action such as agomelatine, a potent agonist of melatonin receptors. Drugs in development for treatment of MDD include triple reuptake inhibitors, dual-acting serotonin reuptake inhibitors and histamine antagonists, and many more. Newer antidepressants have similar efficacy and in general good tolerability profiles. Nevertheless, compliance with treatment for MDD is poor and may contribute to treatment failure. Despite the broad spectrum of available antidepressants, there are still at least 30% of depressive patients who do not benefit from treatment. Therefore, new approaches in drug development are necessary and, according to current research developments, the future of antidepressant treatment may be promising.
Keywords: major depressive disorders, monoamine deficiency, antidepressants, depression

Introduction

Major depressive disorder (MDD) is a common and serious illness with the potential of becoming the leading cause of disability worldwide.[1] The lifetime prevalence rate is 16.2%, and is expected to increase.[2,3] In the elderly, prevalence is about 3% in the general population[4] and 15%–25% among nursing home residents.[5] These numbers may be even higher, because it is estimated that clinically significant depression goes untreated in 60% of the elderly.[6] The average age of onset of MDD is the mid-20s.[3] The lifetime risk in women is twice the risk in men, and is increased during the reproductive years.[3]

The illness is described by a wide range of symptoms, such as disturbances in sleep, appetite, sexual desire, and constipation. It is also characterized by crying, sadness, and loss of the ability to experience pleasure in work or with friends. Depression is strongly associated with suicidal events, cognitive abnormalities, impaired memory function, and slowing of speech and action.[7] Furthermore, patients with MDD often have painful physical symptoms.[8] If symptoms which interfere considerably with activities of daily living and domestic relationships persist for more than two weeks, MDD should be considered.[7]

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Mechanisms of disease

MDD is a complex disorder, probably influenced by genetic and environmental factors. Heritability of depression has been estimated to range from 30% to 40%.[3] The polymorphisms associated with the serotonin transporter gene[9] have been related to more depressive symptoms, diagnosable depression, and tendency to commit suicide.[3,10] Nevertheless, the relationship between genetics and depression is probably very complex and not fully elucidated.[7]

Some environmental factors, such as stress, could predispose to depression by affecting the genome.[7,9] Personality characteristics may predict an individual's susceptibility to depression, but personality may also be modified in the disease. Moreover, personality may alter the clinical presentation of a depressive disorder.[11]

Monoamine deficiency hypothesis

The monoamine hypothesis of depression postulates a deficiency in monoaminergic neurotransmission in the brain, mediated by serotonin and noradrenaline. Noradrenaline depletion may be due to inhibition of tyrosine hydroxylase (see Figure 1), whereas reduced synthesis of serotonin may be due to depletion of dietary tryptophan or mutations of tryptophan hydroxylase.[7,12] Given that reduced serotonin levels do not cause depression in all people, it is unclear if decreased serotonin synthesis is a cause or consequence of depression.[9]

Deficiency in monoaminergic neurotransmission may be caused by disturbed receptor signaling, even with normal monoamine levels. Decreased sensitivity of 5-HT_{1A} and 5-HT_{1B} autoreceptors, which regulate serotonin function, has been associated with depression.[13,14] In contrast, the sensitivity of α_2-noradrenergic receptors, which modulate noradrenaline release by feedback inhibition, was enhanced in depressed patients.[15] Moreover, disturbed receptor signaling could also be a result of malfunction of G-protein or secondary messenger systems, which may impair neurotransmitter function, even without changes in monoamine levels or receptor numbers.[7] Decreased levels of secondary messengers, such as inositol,[7,16] cAMP,[7,17] and cAMP response element-binding protein, have been reported in the brains of patients with MDD at autopsy.[7,18]

The monoamine deficiency hypothesis is supported by the fact that noradrenaline and serotonin reuptake inhibitors have antidepressant activity. Nevertheless, only 50%–70% of patients respond to these drugs, implicating a more complex mechanism for depression.[7,19] Furthermore, dopamine deficiency has been associated with the disease as well. Such a hypothesis is supported by the antidepressant activity of dopamine reuptake inhibitors and dopamine agonists.[7]

Stress, hypothalamic-pituitary-adrenal axis, and growth factors

Stress is perceived by the brain cortex and transmitted to the hypothalamus, where corticotrophin-releasing hormone is produced and released, leading to further elevation of cortisol plasma levels. The hypothalamic-pituitary-cortisol hypothesis postulates that depression is associated with elevated cortisol levels in response to stress.[20,21] However, doubt was cast on this hypothesis by disappointing results in clinical trials with corticotrophin-releasing hormone antagonists.[22] It is also difficult to establish the relationship between stress and depression, given that stress may be both the cause and consequence of depressed mood.[7]

It was suggested that elevated levels of glucocorticoids may reduce neurogenesis and lead to decreased size of the hippocampus in some depressed patients.[23] Stress and cortisol may affect and decrease hippocampal levels of brain-derived neurotrophic factor, necessary for axonal growth, neuronal survival, and synaptic plasticity.[24–26] Reduced brain-derived neurotrophic factor levels were found in the hippocampi of depressed patients.[24]

Other possible disease mechanisms

Other theories about the pathophysiology of depression include changes in glutamatergic neurotransmission,[25] reduced neurotransmission gamma-butyric acid,[26] abnormal circadian rhythms,[27] deficient neurosteroid synthesis,[28] impaired endogenous opioid function,[29] monoamine-acetylcholine imbalance,[30] tyroxine abnormalities,[31] and dysfunction of specific brain structures and circuits.[32] Many of these mechanisms are involved in other psychiatric and neurologic disorders, but the impact on MDD is still unclear.

Traditional therapy

The most common nonpharmacologic approach for treating MDD is psychotherapy. It is especially helpful in patients with a history of childhood adversity or recent stress.[33] Psychotherapy and medication were shown to be comparable for unipolar depression, and it was suggested that psychotherapy may offer a prophylactic advantage compared with medication.[34] Other possible approaches include neurostimulation techniques, electroshock, or electroconvulsive therapy, indicated only for treatment of resistant depression.[9]

Traditional pharmacotherapy includes tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

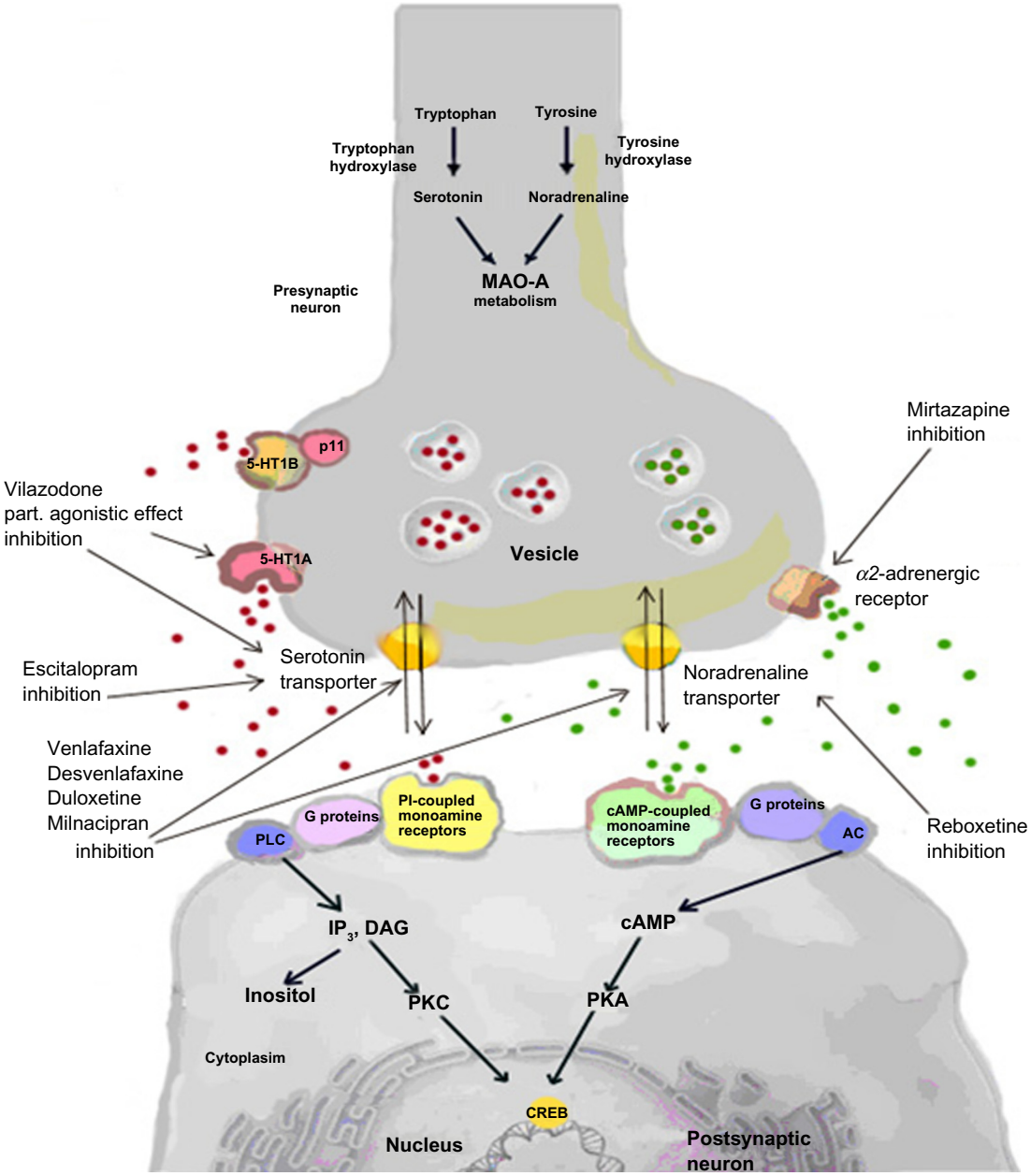

Figure 1 The monoamine deficiency hypothesis.
Abbreviations: MAO-A, monoamine oxidase A; PLC, phospholipase-C; AC, adenylate cyclase; IP_3, ionsitol trisphosphate; PKC, protein kinase c; DAG, diacylglycerol; cAMP, cyclic AMP; CREB, cAMP response element binding.

However, selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants are considered as "first-line" treatment.

Monoamine oxidase inhibitors

MAOIs inhibit MAO-A and MAO-B and reduce monoamine degradation. Phenelzine, isocarboxazid and tranylcypromine are irreversible nonselective inhibitors, and their effect may persist for weeks until the regeneration of MAO. The use of MAOIs is decreasing due to serious side effects, such as acute hypertensive reactions after consumption of tyramine-rich foods, eg, aged cheese.[35] These drugs have severe, potentially life-threatening interactions with many drugs, including meperidine, SSRIs, narcotic medications, and pseudoephedrine.[36] Newer MAOIs inhibit the MAO enzyme reversibly. Moclobemide inhibits MAO-A, and does not require strict dietary restrictions.[39] Selegiline inhibits MAO-B, and its transdermal formulation provides several advantages compared with orally administered MAOIs, including freedom from dietary tyramine restrictions and a better adverse effect profile.[37]

Tricyclic antidepressants

The mechanism of action of most TCAs is noradrenaline and serotonin reuptake inhibition.[38] They also antagonize post-synaptic histamine H_1, α_1, $5HT_{2A}$, and muscarinic receptors.[41] Following oral administration, TCAs are rapidly absorbed. They are highly (90%–95%) bound to plasma albumin, and have large distribution volumes.[41] Metabolism occurs primarily by CYP450 (CYP2D6, CYP2C9, CYP2C19, and CYP3A4), and metabolites are renally excreted.[41] TCAs may interact with SSRIs by inhibition of CYP450 isoenzymes. Concurrent use of fluoxetine or paroxetine can enhance TCA concentrations.[41] Concurrent use of imipramine and clomipramine with MAOIs may cause pharmacodynamic interactions leading to serotonin syndrome.[41] Although widely used in clinical practice, combinations of TCAs with MAOIs and SSRIs are generally considered to be unsafe.[41] TCAs have a small therapeutic range, and therapeutic drug monitoring is useful.[39] Female gender and higher drug doses increase the risk of side effects.[40]

TCAs were shown to be comparable or more effective than SSRIs, but less well tolerated.[41] Their advantage may be efficacy in treatment-resistant depression.[42] Nortriptyline, a potent noradrenaline reuptake inhibitor showed superior pharmacologic properties compared with other TCAs.[41] Nortriptyline was better tolerated and may be administered concomitantly with MAOIs or SSRIs.[41] Clomipramine may be the most efficacious TCA in severe depression.[41] Amitriptyline is considered very effective, whereas dothiepin has the highest toxicity among the TCAs.[41]The more typical atropinic side effects of TCAs[41] are presented in Table 1. Enhanced and toxic concentrations of TCA cause serious adverse effects, such as prolonged intracardiac conduction and postural hypotension.[41,43]

Selective serotonin reuptake inhibitors

SSRIs selectively inhibit neuronal reuptake of serotonin, with no significant affinity for histamine, acetylcholine, or adrenergic receptors. The most frequently used SSRIs in the treatment of depression are fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram.[43] These agents have similar efficacy and tolerability.[44] However, due to pharmacokinetic differences, they are not interchangeable.[45] Sertraline and citalopram show linear pharmacokinetics in contrast with fluoxetine, fluvoxamine, and paroxetine. SSRIs are usually characterized by slow elimination, and it takes time to achieve steady state.[47] Fluoxetine has a half-life of 1–4 days and its active metabolite norfluoxetine 7–15 days. Other SSRIs have shorter half-lives of 1–2 days and no clinically significant active metabolites.[47] SSRIs are extensively metabolized and show high interindividual variability.[47] Fluoxetine and norfluoxetine are inhibitors of CYP2D6[46,47] and CYP3A4.[46] Paroxetine inhibits CYP2D6,[47–49] while fluvoxamine inhibits CYP1A2 and CYP2C19.[48,49] As a consequence, their potential to interact with antipsychotics, opioids, and serotonin-norepinephrine reuptake inhibitors is high.[48] Clinically significant interactions are more likely to occur with fluvoxamine, fluoxetine, and paroxetine compared with citalopram, escitalopram, or sertraline.[48]

Drug interactions with MAOIs, TCAs, moclobemide, tryptophan, lithium, and selegiline, as well as SSRI overdoses, may lead to the serotonin syndrome, characterized by change in mental status, myoclonus, restlessness, hyperreflexia, shivering, diaphoresis, tremor, and possibly death.[47,48] SSRIs cause fewer side effects, such as dry mouth, constipation, and blurred vision, and have a safer cardiac adverse event profile than the TCAs.[47,48] Common adverse effects of SSRIs are listed in Table 1.

Paroxetine is a more potent noradrenaline inhibitor compared with the other SSRIs and has the highest affinity for cholinergic receptors causing typical anticholinergic adverse effects.[48] Sertraline significantly blocks dopamine reuptake, which may result in cardiovascular and extrapyramidal symptoms.[48] Fluoxetine and sertraline have high dopaminergic affinity that may also cause extrapyramidal symptoms. Citalopram has the highest affinity for H_1 receptors of all the SSRIs, and may have weak antihistaminic activity at high doses.[47,48] Despite these adverse effects, SSRIs remain reasonably well tolerated.[44,48]

Newer antidepressants

Newer antidepressants are usually characterized by a dual mode of action, such as inhibition of serotonin, noradrenaline, and dopamine reuptake. The pharmacokinetics, efficacy, and adverse effects of the newer antidepressants will be discussed in detail.

Escitalopram

Escitalopram is the most 5-HT transporter-selective compound and the S-(+)-enantiomer of citalopram.[47] Both SSRIs share similar pharmacokinetics.[22] Following oral administration, escitalopram is rapidly and almost completely absorbed.[48,49] The process is not affected by food.[55] The pharmacokinetic profiles of the newer antidepressants are summarized in Table 2. Escitalopram is widely distributed throughout tissues,[55,56] has low protein binding , and is not likely to have interactions with highly protein-bound drugs.[55]

Table 1 Efficacy and adverse effects of triciclyc antidepressants, serotonin reuptake inhibitors and newer antidepressants

Drug and treatment dose	Efficacy	Common adverse effects
TCA[a]	More efficient than placebo, comparable efficacy to SSRI[b]	Dry mouth, blurry vision, constipation, urine retention, tachycardia, sedation and memory impairment progressing to delirium, seizures and death.[40]
SSRI[b]	More efficient than placebo, comparable efficacy to TCA[a]	Nausea, diarrhea, insomnia, headache, tremor, nervousness and sexual dysfunction.[47,50,51]
Escitalopram 10–20 mg/day	Reponse after 8 weeks 56% in severe depression (MADRS[c] $\geq$ 30).[69] Response after 8 weeks 82.6% and remission 66% after 6 months in severe MDD[d] (MADRS[c])[72] Response and remission of escitalopram 62.1%–68.3% and 51.6%–57.8%, respectively after 8 weeks (MADRS[c])[73,75] Possibly more effective than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine[77] Escitalopram may be suitable in moderate to severe major depression and in adolescents.	Nausea (15%), insomnia (9%), sexual dysfunction (9%), diarrhea (8%), dry mouth (6%) agitation/restlessness, daytime sedation.[45] Possibly better tolerated than duloxetine, paroxetine, raboxetine, sertraline, fluvoxamine and venlafaxine.[77] Adverse event withdrawal rate 3%–7%.[67,72]
Mirtazapine 15–60 mg/day	Responder rate 50%–73% according to HAM-D[e] within 6 months.[102,109-111.] Possibly better efficacy than duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine.[77] Mirtazapine may be superior to SSRI and venlafaxine in the acute phase.[113]	Drowsiness, sedation, insomnia, agitation, restlessness, headache, vertigo, appetite disturbances, changes in body weight, dry mouth, constipation, fatigue.[103] Possibly better tolerated than reboxetine, fluvoxamine, duloxetine amitriptyline possibly less well tolerated than bupropion, citalopram, escitalopram, sertraline, venlafaxine.[77,114] Discontinuation due to adverse effects 4%–5%.[108,109]
Bupropion IR 200–450 mg/day Bupropion XR 150–450 mg/day Bupropion SR 150–400 mg/ day	Similar efficacy as TCA[a] and fluoxetine.[134–136,140] Higher remission rates of bupropion (46%) vs venlafaxine (33%) and similar responder rates (HAM-D[e], MADRS[c]) after 6–8 weeks treatment.[143,144] Bupropion may be suitable to augment citalopram and in major depressions.[146,150]	Bupropion IR: tremor (22%), menstrual complaints (5%), hypertension and impaired sleep (4%).[150] Bupropion SR, XR: headache (22%–24%), dry mouth (13%–16%), sweating (4%–11%), constipation (5%–10%), nausea (9%–10%).[132,143] Discontinuation rates due to adverse events 5%–11%.[118] Seizures, allergic reactions
Venlafaxine IR 75–375 mg/day Venlafaxine ER 75–225 mg/day	At least as effective as TCA[a] and probably more effective than SSRI[b].[168] Similar efficacy as sertraline and escitalopram.[73,75,169] Response odds ratio (1.15) and remission odds ratio (1.19) greater in venlafaxine compared to pooled data from fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine.[168] Remission rates of venlafaxine 45%, after 6–8 weeks.[170] Possibly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine.[77]	Nausea, diarrhea, nervousness, sweating, dry mouth, muscle jerks, sexual dysfunction, blood pressure increase.[45,177] Withdrawal rate due to adverse effects 9%.[75] Discontinuation syndrome: nausea insomnia, chills, irritability and paresthesias. Possibly better tolerated than reboxetine, fluvoxamine, duloxetine, TCA.[77] Poorer tolerability than bupropion, citalopram, escitalopram, sertraline.[77]
Desvenlafaxine 50–100 mg/day	More efficient than placebo at doses of 50 and 100 mg according to HAM-D[e] scores after 8 weeks. Response and remission rates of desvenlafaxine were 53% and 32% respectively.[175,182] No signifficant difference in efficacy between 50 and 100mg.[175]	Nausea, diarrhea, constipation, dry mouth, insomnia, decreased appetite, hyperhidrosis and dizziness ($\geq$10%)[175] ; less common: nervousness, tremor, and increased blood pressure (2%).[45,183] Withdrawal rates due to adverse events 4%–8%.[183]
Duloxetine 40–120 mg/day	Remission rates in patients with severe MDD[d]: 35.9%.[201] Response and remission rates: 58% and 48%, respecitvely, after 8 weeks.[204] Similar efficacy to venlafaxine after 6 weeks treatment.[202] Possibly less efficacious than escitalopram, mirtazapine, sertraline and venlafaxine.[77]	Nausea, dry mouth, constipation, insomnia, dizziness, fatigue, diarrhea, somnolence, increased sweating, decreased appetite ($>$5%).[206] Minimal effect on body weight[208], modest effect on blood pressure and heart rate[209], increased incidence of sexual dysfunction.[210] Better tolerated than reboxetine. Possibly less well tolerated than bupropion, citalopram, escitalopram and sertraline.[77] Withdrawal rates due to adverse events 17%.[204]

(*Continued*)

Table 1 (*Continued*)

Drug and treatment dose	Efficacy	Common adverse effects
Milnacipran 100–200 mg/day	Reponse to treatment after 8 weeks 65% at dose 50 mg/day (HDRS).[222] Response rate 58.9% MADRS[c] and 59.7% HAM-D[e].[222,224] Possibly less efficacious than mirtazapine, escitalopram, venlafaxine, sertraline and citalopram. Possibly more efficacious than bupropion, duloxetine, fluvoxamine, paroxetine, fluoxetine and reboxetine.[77]	Nausea, nervousness, constipation, vertigo (5%), anxiety (4%), hot flushes (3%), dysuria (2%), dizziness, sweating (4%).[45,226] Possibly better tolerated than TCA, reboxetine, fluvoxamine, fluoxetine, mirtazapine, venlafaxine, duloxetine, paroxetine.[77,225] and possibly less well tolerated than bupropion, citalopram, escitalopram, sertraline.[77]
Reboxetine 4–10 mg/day	Response rate in 27 patients with MDD[d], 74% after 6 weeks according to HAM-D[e].[242] In severe MDD[d] responder rate with reboxetine were 56%–74% after 4–8 weeks.[243] Relapse rates afte 46 weeks were 22% (HAM-D)[e].[244] Possibly less efficacious than bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine.[77]	Dry mouth, insomnia, headache, constipation, sweating, nausea, dizziness, anorexia and asthenia (>5%).[240] Male patients: tachycardia, urinary retention or hesitancy, impotence and sexual dysfunction.[240] Frequency of discontinuation was 10%.[245] Possibly less well tolerated than bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine.[77]
Agomelatine 25–50 mg/day	Response to treatment was 56%–63% and remission 30% after 8 weeks (HAM-D[e].[255] Response rate 49% (HAM-D[e]) and improvement in CGI-S[f] after 6 weeks was reported, remission rate 21%.[254]	Nausea dizzines (9%), dry mouth, diarrhea nasopharyngitis (7%) and influenza (7%).[250,254] absence of serotonin syndrome, weight gain and low incidence of sexual dysfunction and gastrointestinal side effects.[250]
Aripiprazole 2–5 mg/day	Remission rates with adjunctive aripiprazole to standard antidepressant treatment vs placebo 25.4% vs 15.2%, response rates 32.4% vs 17.4% respectively after 6 weeks.[262] Mean change in MADRS[c] total score was significantly greater with adjunctive aripiprazole −8.8 than adjunctive placebo −5.8 after 6 weeks.[261]	Akhatisia (23%), nausea (3%), insomnia (8%), restlessness (14%), upper respiratory tract infections (8%), weight gain.[261, 262]

Abbreviations: TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; HAM-D, Hamilton Rating Scale for Depression; CGI-S, Clinical Global Impressions-Severity of illness scale.

Escitalopram is extensively metabolized in the liver via oxidative metabolism.[50,55] In the brain, metabolism of escitalopram propionate may be mediated by MAO-A, MAO-B, and aldehyde oxidase.[51,52] Nevertheless, the metabolites do not contribute appreciably to therapeutic activity.

Escitalopram is a weak inhibitor of CYP isoenzymes 1A2, 2C9, 2D6, and 3A4, and may have a low potential for clinically significant interactions with substrates for these isoenzymes.[55] Ritonavir, a potent CYP3A4 inhibitor, showed no effect on escitalopram pharmacokinetics.[53] In contrast, cimetidine and omeprazole increased escitalopram exposure, but the effect is probably not of clinical concern.[54] Concomitant administration of escitalopram with MAOIs or other SSRIs should be avoided because of possible serotonin syndrome.[55]

The elimination half-life is relatively short compared with other SSRIs, and steady-state plasma concentrations are achieved in a week.[56] The main elimination route is renal.[55]

Escitalopram shows linear and dose-proportional pharmacokinetics in the dose range 10–30 mg/day.[55,56] No reduction of citalopram dosage seems to be necessary in patients with moderately impaired renal function, but may be appropriate in patients with impaired hepatic function.[55] Age and gender showed no clinically significant influence on escitalopram pharmacokinetics.[55,56] Risk factors which may necessitate dose adjustment are presented in Table 3.

Escitalopram may be a suitable first-line antidepressant in moderate to severe major depression[57] and in treatment of depression in adolescents.[58] The drug was shown to be more efficacious than placebo and as least as effective or better than citalopram,[22,66–69] with an early onset of efficacy.[22,59] Differences between the two SSRIs seem to depend on the initial severity of the depressive symptomatology, given that escitalopram has shown superior antidepressive efficacy in severely depressed patients.[60,70] Nevertheless, opposite findings were also reported, suggesting methodologic flaws as a cause for the difference in efficacy between the two drugs.[60] Efficacy scores for newer antidepressants are presented in Table 1.

Escitalopram showed similar efficacy to sertraline[61] and superior efficacy to paroxetine, especially in severely

Table 2 Pharmacokinetic properties of newer antidepressants

Drug	T_{max} (h)	BA[a] (%)	Food	Vd[b]	PB[c]	Metabolism	Interactions	$t_{1/2}$[d] (h)	Ex-cretion	CL[e] (L/h)	SS[f] (days)	PK[g]
Escitalopram	3–4	80	No influence	1100 L	56%	CYP1A2 CYP2C9 CYP2D6 CYP3A4	MAOI SSRI	27–33	Renal	2.7	7	Linear
Bupropion IR Bupropion SR Bupropion XR	1.5 ~3 ~5	87	No influence	19 L/kg	85%	CYP2B6	desipramine venlafaxine carbamazepine lopinavir ritonavir	21			7–10	Linear 300–450 mg
Mirtazapine	1–2.1	50		339 L	85%	CYP1A2 CYP2D6 CYP3A4	carbamazepine phenytoin fluvoxamine paroxetine cimetidine diazepam	20–40	Renal	31	5	Linear 15–75 mg
Venlafaxine Desvenlafaxine	2 2.8	92		6–7 L/kg	27%	CYP2D6 CYP3A4 CYP2C9 CYP2C19	imipramine risperidon	5 11	Renal			Linear 75–450 mg
Duloxetine	6	91	Delays absorption	1943 L	90%	CYP1A2 CYP2D6 CYP2C9	desimipramine CYP2D6 and CYP1A2 inhibitors		Renal	114	3	Linear
Milnacipran	2–6	85%–90%	No influence	5.3 L/kg	13%	CYP3A4	MAOI, tramadol, triptanes, linezolid duloxetine adrenaline noradrenaline	6–7	Renal	37.6	2–3	Linear
Reboxetine	2	94	T_{max} delayed 2–3h	32 L	96%	CYP3A4		13		2.21	4	Linear 1.5–4.5 mg
Agomelatine	1–2	74%		35 L	95%	CYP1A2 CYP2C9 CYP2C19		2–3	Renal			
Aripiprazole	3–5		T_{max} delayed 3h		99%	CYP3A4 CYP2D6	carbamazepine, ketoconazole	75	Renal, fecal		14	

Abbreviations: BA, bioavailability; Vd, volume of distribution; PB, protein binding; $t_{1/2}$, elimination half-life; CL, total clearance; SS, steady-state; PK, pharmacokinetics; MAOI, monamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors.

Table 3 Risk factors which may influence the pharmacokinetics of newer antidepressants

Drug	Factors that may require dose adjustment
Escitalopram	Dose adjustment recommended in patients with impaired hepatic function
Mirtazapine	Age (elderly), hepatic impairment, caution in patients with moderate or severe renal insuficiency
Bupropion	Gender; caution in elderly, and those with renal and hepatic impairment.
Venlafaxine/Desvenlafaxine	Renal and hepatic impairment
	If creatinine clearance is $\leq$ 30 mL/min dose adjustment for venlafaxine recommended
Duloxetine	Hepatic impairment, neccessary dose adjustment.
	Gender, age, nicotine and race – monitor adverse effects, dose adjustment if necessary
Milnacipran	Caution in severe hepatic and moderate to severe renal impairment
Reboxetine	Elderly require lower starting doses
	Caution in renal and hepatic dysfunction
Agomelatine	Caution in patients with hepatic impairment; lack of data about other effects

depressed patients.[62] Furthermore, in short-term studies, superior efficacy of escitalopram compared with citalopram, paroxetine, and duloxetine was observed.[63]

The efficacy of escitalopram was similar to that of venlafaxine, but there was a trend of higher response and remission rates in the escitalopram group.[64,65] The SSRI may be at least as effective as venlafaxine and duloxetine even in severe depression.[66]

Cipriani et al reported superior efficacy of escitalopram over duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Following mirtazapine, escitalopram was the most efficacious drug among 12 antidepressants.[67]

The prominent side effects of escitalopram are similar to those of other SSRIs (see Table 2).[46] Similar tolerability and withdrawal rates for citalopram and escitalopram were reported.[22,67–69] In contrast, escitalopram (10–20 mg/day) showed better tolerability in long-term treatment than paroxetine. The most common adverse event with escitalopram was headache, and nausea with paroxetine.[74] Moreover, nausea, sweating, and obstipation were significantly less frequent compared with venlafaxine.[22,68] Cipriani et al reported better tolerability of escitalopram compared with duloxetine, paroxetine, reboxetine, sertraline, fluvoxamine, and venlafaxine.[79]

Doses of 10–20 mg/day showed consistent antidepressive efficacy and excellent tolerability in primary care patients with MDD.[68] The recommended starting dose of 10 mg/day is appropriate for most patients regardless of age, gender, or mild to moderate renal impairment or hepatic insufficiency.[55] A period of at least four weeks is worthwhile before considering further intervention. If 10 mg/day is not effective, an increase to 20 mg/day should be considered.[69,70]

Mirtazapine

The antidepressant activity of mirtazapine is a result of enhanced serotonergic and noradrenergic neurotransmission through blockade of presynaptic α_2-adrenergic autoreceptors and heteroreceptors and postsynaptic 5-HT_2 and 5-HT_3 receptors.[71,72] No influence on serotonin or noradrenaline reuptake was observed.[73,84] Mirtazapine has low affinity for central and peripheral dopaminergic and muscarinic receptors, and high affinity for H_1 receptors.[83,84]

Following oral administration, mirtazapine is rapidly absorbed, but the absolute bioavailability is moderate (see Table 2).[73] The drug is nonspecifically and reversibly bound to proteins and possess a high distribution volume.[75,86] Metabolism is mediated by CYP1A2, CYP2D6, and CYP3A4.[75,87] Demethylmirtazapine is the active metabolite, but its exposure in the human body is three times lower compared with the parent drug.[74]

Low inhibitory effects of mirtazapine on major CYP isoenzymes were reported *in vitro*.[83,88] No significant interactions with the CYP2D6 substrates amitriptyline, clozapine, olanzapine, and risperidone were observed.[90–92] In contrast, plasma concentrations of mirtazapine were reduced after concomitant administration of the CYP3A4 inducers carbamazepine[87,90] and phenytoin.[75] Moreover, mirtazapine disposition was affected by fluvoxamine and, to a lesser extent, by paroxetine.[76,77] Coadministration of cimetidine (an inhibitor of CYP3A4, CYP1A2, and CYP2D6) increased mirtazapine plasma concentrations significantly, requiring dose adjustment.[78] An additive sedative effect was observed with diazepam. Moreover, patients should be advised to avoid alcohol while taking mirtazapine.[83,87]

The drug is predominantly excreted in the urine and feces.[87,89] The activity is prolonged by the circulation of the parent compound.[87,89] High clearance values indicate renal tubular secretion.[83,87,89] The elimination rate is strongly affected by CYP2D6 polymorphism.[79,80] Steady state is reached in less than a week.[81]

In the therapeutic range, mirtazapine shows linear pharmacokinetics.[99] Nicotine may decrease plasma mirtazapine

levels, and smokers may require increased doses.[82] In contrast, mirtazapine plasma levels are increased in the elderly,[91,100] as well as in patients with hepatic impairment,[87] and dose reduction should be considered in both groups. Mirtazapine exposure in patients with severe or moderate renal insufficiency is increased compared with healthy controls.[83] Although there are no differences in reported adverse effects,[102] the drug should be used with caution in these patients.[84] Gender affects mirtazapine plasma levels, but the changes are not clinically important (see Table 3).[101]

The efficacy of mirtazapine in treatment of patients with moderate to severe MDD was reported in several studies.[104–106] Short-term studies revealed similar efficacy for mirtazapine and amitriptyline.[107–109] Moreover, mirtazapine had a longer time to relapse than amitriptyline during the first 20 weeks (see Table 1).[85]

Furthermore, mirtazapine showed similar or greater efficacy than citalopram, fluoxetine, paroxetine, sertraline, duloxetine, fluvoxamine, and reboxetine.[79,111–114] In a meta-analysis of 25 randomized, controlled trials, mirtazapine showed a faster onset of action than SSRIs and was superior for short-term (two-week) response and remission rates, but the differences were not significant at the end of acute-phase treatment (6–12 weeks).[86] The efficacy of mirtazapine and venlafaxine were similar in patients with severe depression characterized by melancholic features.[87]

Mirtazapine was generally well tolerated in patients with MDD, with a lower frequency of side effects compared with placebo (see Table 1).[84,96,105] Sedation, especially at low dose, and weight increase may be due to H_1-receptor blockade.[105] In a long-term treatment study, weight gain was the only more frequent side effect with mirtazapine than placebo, whereas blood pressure and heart rate were similar.[83,110,117]

Compared with amitriptyline, mirtazapine had fewer adverse events and less need for discontinuation of treatment due to an adverse event.[83,110] Dry mouth, vertigo, and weight increase were as frequent as with TCAs, but seizures were less frequent.[22,84]

Discontinuation rates due to adverse events for mirtazapine and SSRIs were similar. Mirtazapine was associated with significantly less insomnia, sexual dysfunction, and nausea than SSRIs, but with significantly more weight gain, dry mouth, fatigue, and excessive somnolence.[88] Adverse effects such as increased salivation and weight gain were more frequent with mirtazapine compared with venlafaxine but sweating, constipation, increased sexual desire, and weight loss were more common with venlafaxine.[116]

Mirtazapine is used as a single agent, or in combination with SSRIs or venlafaxine. The recommended dose is 15–45 mg/day, and it is generally given as a single dose in the evening.[46]

Bupropion

Bupropion is an atypical antidepressant, probably a selective inhibitor of noradrenaline and dopamine reuptake. Bupropion and its metabolites are slightly more potent inhibitors of dopamine than of noradrenaline reuptake, and do not affect the release or transport of other neurotransmitters, or have appreciable affinity for postsynaptic receptors including histamine, α-adrenergic, serotonin, dopamine, or acetylcholine receptors.[89,90]

Bupropion is available in three oral formulations, ie, immediate-release (IR), sustained-release (SR), and extended-release (XR).[91] Absorption rates vary between the formulations, but there is no significant difference in the extent of absorption.[120] Food does not affect absorption, which is at least 87% of an administered dose.[120] Pharmacokinetics are linear in the therapeutic range (see Table 2).[120,121]

Bupropion is extensively distributed and bound to plasma proteins.[121] Following hepatic metabolism via CYP2B6, three active metabolites, ie, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion are formed.[92,93] Hydroxybupropion and threohydrobupropion possess about 50% of the activity of the parent drug[123] and their plasma concentrations are 4–7-fold and ~5-fold higher than bupropion, respectively.

Major effects of CYP2B6 genetic polymorphisms on the pharmacokinetics of bupropion have not been shown.[94] However, concomitant administration of CYP2B6 inducers, such as carbamazepine, lopinavir, and ritonavir, decreased bupropion plasma levels.[90,95,96]

Bupropion and hydroxybupropion may have a low potency for inhibition of CYP2D6.[123] Coadministration of bupropion with the CYP2D6 substrates desipramine and venlafaxine resulted in increased levels of the substrates.[90,97] A case of severe bradycardia was related to the addition of bupropion to metoprolol.[98] Therefore, low doses should be used, and dose monitoring should be considered following concomitant administration of bupropion and CYP2D6 substrates with a narrow therapeutic range.[90]

The activity of bupropion is prolonged as a result of slow elimination of metabolites.[121] Steady-state concentrations are reached after 7–10 days.[121] Renal excretion is predominant, but the drug and its active metabolites cross the blood-brain barrier and placenta, and are also excreted in human breast milk.[120]

The pharmacokinetic properties of bupropion are probably not influenced by nicotine.[99,100] However, the effect of gender is unclear due to controversial findings.[129–131] Bupropion SR is metabolized more rapidly in children compared with adults,[121] and the elderly are at risk of accumulation of the drug and its metabolites.[101] Slower elimination of bupropion was observed in patients with renal impairment,[102] and high variability in pharmacokinetic parameters was observed in patients with hepatic impairment. Therefore, bupropion should be used with caution in these groups (see Table 3).[121]

Bupropion was shown to be more efficacious than placebo. Improvement in primary and secondary outcomes were observed after 6–8 weeks with all bupropion formulations in adults with moderate to severe depression.[103,104 ,120]

Bupropion IR showed similar efficacy to nortriptyline,[105] amitriptyline,[106] and fluoxetine.[107] No significant differences in efficacy were observed with bupropion SR and sertraline after 8–16 weeks[139–141] or fluoxetine.[108] In the elderly, bupropion SR and paroxetine showed similar efficacy.[109] There were no significant differences between bupropion XR and escitalopram[110] or venlafaxine XR[111,112] in terms of primary or secondary outcome measures. After switching from citalopram, bupropion SR was as effective as sertraline and venlafaxine XR.[113] The drug was as effective as buspirone in augmentation of citalopram (see Table 1).[114]

Different formulations of bupropion have similar tolerability profiles and are generally well tolerated in adults and the elderly.[120] Most adverse events associated with bupropion are mild to moderate in severity (see Table 1).[120,134,135]

Allergic reactions to bupropion occur rarely but, if symptoms arise, drug discontinuation should be advised.[115,120] The risk of seizures is dose- but not formulation-dependent.[120] Rate of seizures was 0.1% for doses of 100–300 mg/day, and increased to 0.4% at doses of 300–450 mg/day.[120,125,149] Adverse events resulting in discontinuation of therapy were agitation, headache, nausea, and rash, which occurred at a rate of approximately 5%–11% with all bupropion products.[149]

Compared with nortriptyline, bupropion was associated with significantly fewer adverse events such as dry mouth, somnolence, and tachycardia.[136] Generally, the tolerability profiles of bupropion and SSRIs are similar, although bupropion is associated with more headache and dry mouth.[115,120] However, sexual dysfunction following SSRIs is not a problem with bupropion,[151] and lower rates of somnolence and diarrhea are associated with this agent.[151] Similar incidences of adverse events were reported for bupropion and venlafaxine.[145]

The administration of bupropion has certain advantages, such as a greater reduction in severity of symptoms and fewer adverse events.[148] Bupropion is indicated in the treatment of adult patients with major depression but is not approved for use in pediatric patients.[149] The recommended initial doses are 100 mg of bupropion IR twice daily, 150 mg of bupropion SR once daily, and 150 mg of bupropion XR once daily.[115,120] The maximum recommended dose is 450 mg/day for IR (150 mg three times daily) and XR (450 mg in the morning) formulations, or 400 mg/day of bupropion SR (200 mg twice daily).[120,152]

Venlafaxine and desvenlafaxine

Venlafaxine probably inhibits serotonin uptake only in low doses, whereas both serotonin and noradrenaline uptake are inhibited following high doses.[115] The drug does not possess significant affinity for $5HT_{1A}$, $5HT_{2A}$, D_2, muscarinic, or α_1- or α_2- receptors, and does not inhibit MAO.[116,153] Desvenlafaxine (O-desmethylvenlafaxine), the major metabolite of venlafaxine, has similar potency for the inhibition of serotonin and noradrenaline uptake.[153]

Following oral administration of venlafaxine, absorption starts after approximately 20 minutes and is completed within three hours for venlafaxine IR and for desvenlafaxine.[116,117] Venlafaxine XR is absorbed more slowly, but the extent of absorption is similar between formulations.[156]

The drug is widely distributed in the body, with low protein binding and a high volume of distribution (see Table 2).[118,119] Following oral absorption, venlafaxine undergoes extensive first-pass hepatic metabolism, where conversion to the active metabolite, desvenlafaxine, occurs via demethylation.[157] This reaction is mediated by CYP2D6.[120] Desvenlafaxine is further metabolized by CYP3A4.[122] Other metabolic pathways for venlafaxine include N-demethylation which is probably mediated by CYP3A4.[157] CYP2C9 and CYP2C19 isoenzymes may also be involved in the metabolic pathways of both drugs.[121]

In contrast with desvenlafaxine, the CYP2D6 genetic polymorphism has a significant influence on venlafaxine pharmacokinetics.[122] Both drugs may have low potential for drug interactions, because of low protein binding and a relatively weak inhibitory effect on CYP isoenzymes.[90,123] Nevertheless, increased plasma levels of imipramine, its metabolite desimipramine,[124] and risperidone were associated with concomitant administration of venlafaxine.[125] Furthermore, diphenhydramine may alter the disposition of venlafaxine via inhibition of CYP2D6.[126] CYP3A4 inducers may enhance the clearance rate of desvenlafaxine.[122]

Venlafaxine and desvenlafaxine are primarily excreted via the renal route.[157,127] About 29% of a venlafaxine dose is excreted as the active metabolite.[156,128] Both venlafaxine and

desvenlafaxine are rapidly eliminated, and steady-state plasma concentrations are reached within three days. Both drugs show linear pharmacokinetics in the therapeutic range.[157]

Age and gender differences are not clinically significant and require no dose adjustment for either drug.[129] Disposition of venlafaxine and desvenlafaxine may be affected by renal impairment, and a reduction in venlafaxine dose is recommended for patients with creatinine clearance rates <30 mL/min.[157,166] Moreover, due to altered metabolism, patients with mild to moderate hepatic impairment require dose adjustment of venlafaxine and desvenlafaxine (see Table 3).[157]

Superior efficacy of venlafaxine compared with placebo and efficacy similar to that of the TCAs in major depression was reported.[22,130,131] However, venlafaxine was superior to TCAs in treatment-resistant depression.[170] Controversial reports exist concerning the relative efficacy of venlafaxine and SSRIs. Comparison of venlafaxine with sertraline and escitalopram showed similar efficacy in the treatment of severe depressive disorders.[76,80,132] Comparable efficacy has also been reported for venlafaxine, fluoxetine, paroxetine, and fluvoxamine.[22,133] However, some authors observed superior efficacy of venlafaxine compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine (see Table 1),[79,134,135] while others found only increased efficacy compared with fluoxetine among the second-generation antidepressants.[136] Higher remission rates were observed with venlafaxine compared with SSRIs and placebo.[172] Long-term venlafaxine treatment was effective in reducing relapse after a major depressive episode.[170]

Despite the conflicting evidence, venlafaxine may be a cost-effective alternative to fluoxetine and amitriptyline when used as first-line therapy.[137] Venlafaxine XR is also probably one of the best alternatives for patients who do not benefit from SSRIs.[46,172] Overall response and remission rates in major depression were significantly better with desvenlafaxine 50–100 mg compared with placebo.[138]

Venlafaxine is better tolerated than TCAs, but may cause a broader array of adverse events, such as dry mouth, constipation, increased pulse, and increased heart rate compared with the SSRIs.[46,139] The blood pressure increase seems to be dose-dependent, and ranges from 2% at doses of 75–150 mg/day to 10% for 300 mg/day.[22,140,178] Discontinuation syndrome, characterized by nausea, insomnia, chills, irritability, and paresthesias may occur when venlafaxine is stopped abruptly (see Table 1). This syndrome may be suppressed by switching to fluoxetine or tapering venlafaxine prior to withdrawal.[140] Furthermore, overdose with venlafaxine may be more serious than with the SSRIs.[46,141] Tolerability is dose-dependent and may be improved by slower titration to higher doses.[142]

Desvenlafaxine has an acceptable safety and tolerability profile.[143] A strong dose-response effect on tolerability was reported, but both 50 mg and 100 mg doses were well tolerated.[144,177] Discontinuation rates due to adverse events were similar to those with placebo. The most common adverse event was transient mild to moderate nausea. Changes in mean blood pressure were small but statistically significant. Erectile dysfunction in man and anorgasmia in women were the most common sexual adverse events.[144]

The usual dose of venlafaxine IR is 75–375 mg/day and 75–225 mg/day for venlafaxine XR.[46] With rapid venlafaxine dose escalation up to 375 mg/day, onset of efficacy can be achieved after only one week.[145] Use of higher doses may also improve response in treatment-resistant depression. However, higher venlafaxine doses (300–375 mg/day) were associated with poorer tolerability.[182] The usual dose of desvenlafaxine ranges from 50–100 mg once daily, although doses higher than 50 mg showed no evidence of better efficacy.[46,184]

Duloxetine

Duloxetine is an inhibitor of serotonin and noradrenaline reuptake, with more than 100-fold greater potency compared with venlafaxine.[146] Duloxetine has low affinity for D_2, serotonin, α_1- and α_2-adrenergic, muscarinic, H_1, and opioid receptors. Duloxetine does not inhibit gamma-amino butyric acid, choline transporters, MAO-A or MAO-B.[187]

Duloxetine is absorbed within six hours following oral administration.[147] This process may be delayed by food and decreased by evening administration.[148] The drug has high protein binding and a high volume of distribution (see Table 2).[149,150]

Extensive metabolism, predominantly via CYP1A2, to a lesser extent via CYP2D6, and at a very low rate via CYP2C9,[151,152] has been reported, but the metabolites have no significant activity.[153] Duloxetine is a moderate CYP2D6 inhibitor and may inhibit its own metabolism[154,155] as well as the metabolism of CYP2D6 substrates, such as desimipramine.[90,195] The inhibition or induction of CYP1A2 is not clinically important , and coadministration of duloxetine with CYP1A2 substrates does not necessitate their dose adjustment.[193] However, potent inhibitors of CYP2D6 and CYP1A2 may result in enhanced duloxetine concentrations and a need for dose adjustment.[191,193]

Due to high protein binding, duloxetine may displace other extensively protein-bound drugs, such as warfarin.[191] Elimination of the drug is rapid and primarily via urine and

feces.[192] Steady state is reached in three days.[190] Duloxetine has linear pharmacokinetics in the therapeutic range.[194]

Female gender and nicotine use have been associated with higher duloxetine plasma levels.[196] Hispanic patients had a higher volume of distribution and delayed absorption compared with non-Hispanics.[196] Clearance decreases with increasing age, although this effect is small.[196] Hepatic impairment decreases the clearance of duloxetine, and dose adjustment is necessary in patients with liver disease (see Table 3).[156]

At doses of 40–120 mg/day, duloxetine shows superior efficacy compared with placebo in short-term studies (≤15 weeks).[198–201] The efficacy of duloxetine in the treatment of painful somatic vegetative symptoms in patients with MDD is questionable.[157,158]

Duloxetine had better efficacy than paroxetine or fluoxetine only in patients with severe depression (see Table 1).[159] The drug showed no significant difference in efficacy compared with venlafaxine,[160] but a lower risk of increased blood pressure and fewer discontinuation symptoms when treatment was stopped.[204,161] Compared with escitalopram, similar onset and efficacy of duloxetine (60–120 mg/day) has been observed.[162,163] In contrast, a meta-analysis reported that escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine.[79]

Generally, duloxetine is well tolerated both in short-term and long-term treatment of MDD (see Table 1).[179,191,199,201] The incidence of most common side effects may be dose-dependent.[164] Long-term treatment has a minimal effect on body weight,[165] whereas short-term treatment is associated with modest effects on blood pressure and heart rate, no clinically significant effect on Electrocardiogram profiles,[166] an increased incidence of sexual dysfunction,[167] and an increased risk of higher serum transaminase levels.[209]

The safety and tolerability profile of duloxetine 40–120 mg/day is similar to that of paroxetine 20 mg/day.[168] However, duloxetine is less well tolerated than escitalopram.[207,208] Patients on duloxetine experience higher rates of insomnia and constipation.[207] Furthermore, Cipriani et al reported poorer tolerability of duloxetine compared with sertraline.[67] Higher discontinuation rates were observed with duloxetine due to adverse events compared with venlafaxine. Nausea and dizziness were more frequent in patients on duloxetine, while patients on venlafaxine experienced significantly greater elevation of systolic blood pressure.[204]

The usual starting dose is 40 mg/day (20 mg twice daily) to 60 mg/day (30 mg twice daily or 60 mg once daily) in the US and 60 mg once daily in the European Union.[191]

Milnacipran

Milnacipran inhibits noradrenaline and serotonin uptake at presynaptic sites.[169] Despite the high affinity for both serotonin and noradrenaline transporters, noradrenaline reuptake is preferentially blocked.[170] Postsynaptic cholinergic, adrenergic, H_1, D_2, and serotonergic receptors are not affected.[171,172]

Following oral administration the onset of absorption is delayed.[173] Bioavailability is high and not affected by food.[174,218] Milnacipran has low protein binding and extensive distribution in the body.[219,174] The drug undergoes oxidative biotransformation via CYP3A4 and conjugation.[219] Only one of three metabolites has pharmacologic activity, but the concentrations are <1% of the parent compound. The risk of pharmacokinetic drug-drug interactions may be low.[175,219] Moreover, induction or inhibition of CYP2D6 or CYP2C19 has no significant effect on milnacipran.[175]

Due to potential pharmacodynamic interactions, milnacipran is contraindicated in patients receiving MAOIs. Concomitant administration of drugs that may influence serotonin metabolism, such as tramadol, triptanes, and linezolid, is not recommended or requires caution due to potential serotonin syndrome. Coadministration with digoxin may result in potentiation of hemodynamic effects, whereas coadministration with adrenaline and noradrenaline may be associated with paroxysmal hypertension and possibly arrhythmia.[218]

Milnacipran elimination is rapid and predominantly renal.[218,219] Steady-state concentrations are reached within a few days.[215,221] The drug shows linear pharmacokinetics over the therapeutic dose range (see Table 2).[218]

Age and gender influence milnacipran plasma levels but dose adjustment is not necessary.[218] Milnacipran should be administered with caution in patients with severe hepatic or moderate to severe renal impairment (see Table 3).[176,215,218,220]

Milnacipran 50 mg was significantly more effective than placebo in the treatment of MDD.[176,177] Comparison of milnacipran with other antidepressants, such as SSRIs and TCAs, demonstrated no significant differences in clinical response or remission rates in the acute phase.[178,179] Cipriani et al reported better scores for mirtazapine, escitalopram, venlafaxine, sertraline, and citalopram, than for milnacipran. In contrast,

milnacipran scored better than bupropion, duloxetine, fluvoxamine, paroxetine, fluoxetine, and reboxetine.[67]

Milnacipran is generally well tolerated (see Table 1).[180,226] Milnacipran may be superior to TCAs and SSRIs in terms of need for premature treatment withdrawal due to adverse events. Patients who experienced adverse effects from other antidepressants in the acute phase of treatment may benefit from this drug.[228]

Cipriani et al reported better tolerability scores for escitalopram, sertraline, bupropion, and citalopram compared with milnacipran. In contrast, milnacipran scored better than mirtazapine, fluoxetine, venlafaxine, duloxetine, fluvoxamine, paroxetine, and reboxetine.[67]

The usual dose range for milnacipran is 100–200 mg/day.[46] Titration of the dose is recommended. The initiation dose should be 12.5 mg on the first day and 12.5 mg twice daily on the second and third days, 25 mg twice daily on the fourth to seventh days, and 50 mg twice daily thereafter. Based on individual response, the dose should be increased to 100 mg twice daily.[218]

Reboxetine

Reboxetine is a potent, selective, and specific noradrenaline reuptake inhibitor, with negligible affinity for muscarinic, H_1, α_1, and D_2 receptors.[180]

Reboxetine has two chiral centers, but only the (R,R)-(−)- and (S,S)-(+)-enantiomer is present in the marketed product. Some studies suggest that both the therapeutic and adverse effects are related predominantly to (S,S)-(+)-reboxetine.[181]

Reboxetine is absorbed rapidly and almost completely after oral administration.[182,183] Food delays but does not influence the extent of absorption (see Table 2).[184] Reboxetine is extensively bound to plasma proteins and has a moderate distribution volume compared with other antidepressants.[231–233] Metabolism occurs principally via CYP3A4.[231] Each enantiomer is metabolized to the primary metabolite O-desethylreboxetine, and three other metabolites.[185] Reboxetine is probably not an inhibitor of CYP isoenzymes.[186,231]

The drug has a moderate half-life and low clearance.[231,232] Reboxetine exhibits linear pharmacokinetics in the therapeutic range.[231] After multiple doses, steady state is achieved within four days.[231]

Ethnicity seems to influence reboxetine pharmacokinetics but dose adjustment is not necessary.[186] Plasma levels are higher and more variable in elderly patients, and therefore treatment with reboxetine should be initiated at a lower dose.[187,188] The elimination rate of reboxetine decreases as renal function declines.[189] Elimination is also slower in patients with hepatic dysfunction, but the degree of dysfunction does not affect reboxetine pharmacokinetics (see Table 3).[190]

In short-term studies (4–6 weeks) reboxetine showed superior efficacy compared with placebo in primary and secondary outcomes.[242–244] Overall, reboxetine scored significantly better in mean responder rate and relapse rates compared with placebo (see Table 1).[191,192,242] Compared with imipramine, the efficacy of reboxetine was similar in adults[193] and elderly patients,[194] but reboxetine had significant advantages in the treatment of melancholic patients.[195] Similar efficacy of reboxetine and fluoxetine was reported, but reboxetine was more effective in a subgroup of severely depressed patients.[196,197] Moreover, social functioning was better in patients who achieved remission with reboxetine.[250]

Nevertheless, Cipriani et al suggested that reboxetine was significantly less effective than bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, and venlafaxine.[79]

The drug showed a good safety and tolerability profile (see Table 1).[242] Reboxetine and imipramine had similar tolerability in adults and the elderly. Frequency of discontinuation due to adverse events was lower in the reboxetine group, whereas cumulative risk of hypotension, dry mouth, and tremor was significantly higher in the imipramine group.[247] Reboxetine patients had a lower risk of serious adverse events, adverse event-related withdrawals, and treatment-related adverse events.[248] The overall score of reboxetine for safety and tolerability was better than TCAs.

The adverse event profile of reboxetine is different to that of the SSRIs. Patients on reboxetine experienced less agitation, nervousness, anxiety, and gastrointestinal events compared with those on fluoxetine. Reboxetine was not associated with an increased risk of seizures, orthostatic hypotension, or cardiotoxicity,[250] but had poorer tolerability than other antidepressants, including bupropion, citalopram, escitalopram, fluoxetine, and sertraline.[79]

Nevertheless, reboxetine is considered safe when administered at doses of 8–10 mg/day to adult (18–65 years) and at 4–6 mg/day to elderly (>65 years) patients.[242]

The recommended therapeutic dose for adults is 4 mg twice daily (8 mg/day). The dose can be increased to 10 mg/day after three weeks if there is an inadequate clinical response. The recommended dose for the elderly (>65 years) is 2 mg bid (4 mg/day) and, if necessary, the dose can be increased

to 6 mg/day. The same strategy is used for patients with renal impairment or moderate to severe hepatic insufficiency.[242]

Agomelatine

Agomelatine is an antagonist of serotonin $5HT_{2B}$ and $5HT_{2C}$ receptors and a potent agonist of melatonergic MT_1 and MT_2 receptors.[198,199] Serotonin outflow is not affected, but due to $5HT_{2C}$ antagonism, overflows of dopamine and noradrenaline are produced in the frontal cortex.[200] The drug received marketing authorization for Europe in 2009 and is awaiting Federal Drug Administration approval in the US.

After oral administration, more than 78% of the dose is rapidly absorbed.[254] Agomelatine is highly protein-bound and moderately distributed (see Table 2).[253]

Metabolism to inactive hydroxylated and demethylated metabolites is mediated primarily by CYP1A2 and to a less degree by CYP2C9 and CYP2C19.[201] There is a lack of data about potential drug interactions, and this requires further investigation. The metabolites are excreted mainly in urine and feces.[253,254] Elimination rate is very fast and steady-state concentrations are reached rapidly.[253]

The bioavailability of agomelatine may be increased in women and reduced in smokers.[255] There are limited data about the pharmacokinetics of agomelatine in the elderly and in patients with renal impairment. Nevertheless, systemic exposure to agomelatine is increased in patients with hepatic impairment (see Table 3).[253,255]

Agomelatine significantly improved response rates and time to first response compared with placebo in 212 outpatients who received 25 or 50 mg/day.[202] Moreover, the onset of response with agomelatine was faster (two weeks) compared with paroxetine (four weeks).[203] Higher efficacy than placebo was observed in patients with severe depression and efficacy increased with increasing severity of depression.[204] Agomelatine 50 mg/day and venlafaxine 75–150 mg/day had similar response rates after 6–12 weeks.[205,206]

Agomelatine was generally well tolerated, with a good safety profile (see Table 1).[256] Compared with venlafaxine, the agomelatine treatment group experienced less frequent sexual dysfunction and orgasmic dysfunction.[259] Safety profile was generally better compared with current standard treatments, including absence of serotonin syndrome, weight gain, and a low incidence of sexual dysfunction and gastrointestinal adverse effects.[252] Abrupt cessation of agomelatine was not associated with discontinuation symptoms.[207]

Despite encouraging results for the safety and tolerability of agomelatine, there is still a lack of data regarding its efficacy which requires further investigation. The usual initiating dose is 25 mg/day which may be increased if necessary to 50 mg/day.[253]

Aripiprazole

Aripiprazole is an atypical antipsychotic approved as a adjunct treatment for MDD. The probable mechanism of antidepressant action is partial agonism at D_2, D3, and $5\text{-}HT_{1A}$ receptors and antagonistic activity at $5\text{-}HT_{2A}$ receptors. Moderate affinity was also found for D4, $5\text{-}HT_{2C}$, $5\text{-}HT_7$, α1-adrenergic, and H_1 receptors, whereas the activity at muscarinic and cholinergic receptors was minimal.[208]

Aripiprazole is well absorbed following oral administration. Food prolonged the time of absorption for approximately three hours but did not affect extent of absorption (see Table 2). The drug is almost completely bound to plasma proteins. Following metabolism mediated by CYP3A4 and CYP2D6, the active metabolite, dehydroaripiprazole, is formed. Genetic polymorphism of CYP2D6 has a significant influence on aripiprazole plasma levels, and poor metabolizers have an approximately 60% increased exposure to the drug. Aripiprazole has low inhibitory potential for CYP450 isoenzymes. No relevant interactions were observed after coadministration of the drug with SSRIs and venlafaxine. In contrast, concomitant administration of CYP3A4 inducers may require increased doses of aripiprazole whereas concomitant administration of CYP2D6 or CYP3A4 inhibitors may require dose reduction for aripriprazole.[262]

Aripiprazole is eliminated slowly, therefore takes about two weeks to reach steady state. Urine and feces are the main elimination routes.[262] Age, race, gender, smoking status, and hepatic and renal function showed no clinically relevant effects on aripiprazole pharmacokinetics.[262]

A meta-analysis of clinical efficacy trials of aripiprazole (2–20 mg/day) revealed increased response rates of 8% and increased remission rates of 10% when the drug was used as adjuvant antidepressant medication compared with placebo in patients with MDD (see Table 1).[209,210] However, the absolute difference in the efficacy outcome between aripiprazole and placebo was relatively low, and therefore the clinical significance of the findings is debatable.[211,212] Because augmentation is used in patients who have failed to respond to monotherapy, evaluation of clinical relevance is difficult and further studies are necessary.

The most common adverse effects of aripiprazole are presented in Table 1. Discontinuation of treatment due to

adverse effects was rarely observed, and no serious adverse effects were reported.[263,264]

The starting dose for adjunctive aripiprazole treatment should be 2–5 mg/day. If necessary, a weekly dose increase is recommended up to 15 mg/day. The drug is not approved for the treatment of patients with dementia-related psychosis or depressive pediatric patients.[262] Further investigations with aripiprazole are necessary to establish its full potential in the treatment of MDD.

Emergence of new therapeutic agents

Vilazodone is a serotonin reuptake inhibitor and a partial 5-HT_{1a} agonist. This drug is currently under clinical evaluation for the treatment of major depression and awaiting approval by the Federal Drug Administration. So far, results for the clinical efficacy of vilazodone in depressed patients have been conflicting. A large Phase II trial including more than 1000 depressed patients failed to show efficacy of the drug over placebo.[213] In contrast, a Phase III trial which included 410 patients with MDD revealed superior efficacy of viladozone (10–40 mg/day) over placebo in primary and secondary outcomes within eight weeks.[214] Vilazodone was well tolerated, and adverse effects were mild to moderate, including nausea, somnolence, diarrhea, and dizziness.

Serotonin, noradrenaline, and dopamine (triple) reuptake inhibitors are in process of development,[215] and most are now in Phase II clinical trials.[216] Some of these drugs (eg, DOV 21947) show significantly higher efficacy compared with placebo and similar efficacy to citalopram.[269] In contrast, lack of improved efficacy resulting in discontinued development (NS-2359) was also reported.[217]

Drugs that antagonize α_2-adenoreceptors and suppress reuptake of serotonin or noradrenaline or both (S35966 and R226161) may have a faster onset of effect, and improve cognition and sexual function. However, adverse effects comprising increased arterial pressure and tachycardia were reported.[218,219,267]

Dual-acting serotonin reuptake inhibitors and H_3 antagonists (eg, JNJ-2583867) may improve mood and cognitive impairment in depression and have a low risk of obesity. A possible disadvantage of these substances may be their wake-inducing action.[220,267]

Some emerging evidence suggests that several families of glutamate receptors may be potential targets for new antidepressants.[267,269] CP-10-606, an N-methyl-D-aspartic acid antagonist, significantly improved depressive symptoms compared with placebo.[269] There are some suggestions that positive allosteric modulators at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors may be useful in the clinical management of depression.[267,269] However, clinical data on these agents are not yet available.[269]

Riluzole, a glutamate-modulating agent, approved for treatment of amyotrophic lateral sclerosis, showed antidepressant properties and was well tolerated.[221,269] However, its role as monotherapy or augmentation of standard therapy remains to be established.

Metyrapone, an inhibitor of cortisol synthesis, may become a possible adjunctive agent for major depression.[269] Also, a strong antagonist of the Type II glucocorticoid receptor, mifepristone (RU486) was suggested as adjunctive treatment for psychotic depression.[269] However, pivotal Phase III studies of mifepristone in MDD with psychotic features have had discouraging results.[269]

Compliance

One of the major obstacles to effective management of depression is poor compliance.[220] Sawada et al found that only 44.3% patients continued antidepressant treatment after six months. Moreover, 63.1% patients who discontinued therapy did so without consulting their physicians.[221]

Reasons for treatment discontinuation are multifactorial. Symptoms of depression such as poor concentration and motivation may predispose patients to noncompliance. Early withdrawals are usually due to adverse events or lack of efficacy. However, later dropouts are usually due to patients feeling better or fearing drug addiction. Studies suggest men are more likely to discontinue antidepressant therapy than women following initial treatment efficacy.[276]

Choice of an adequate, effective, and well tolerated drug with optimal formulation, as well as effective communication between patient and health professionals, are important for successful treatment. The newer, more selective antidepressants may have better tolerability and hence better compliance.[277] Moreover, drugs with a longer half-life and once-daily dosing schedules will improve patient compliance.[276,277] Patients suggest that information about adverse events and likely duration of treatment may significantly improve compliance. Well informed patients are less likely to discontinue treatment and more likely to switch drug if necessary.[222,223]

Conclusion

MDD is a complex disease and requires a multifaceted approach for research, diagnosis, and treatment. Modern classes of antidepressants such as SSRIs, serotonin/noradrenaline reuptake inhibitors, and noradrenaline/dopamine reuptake inhibitors offer superior tolerability and safety over older medications like the TCAs and MAOIs. However, the choice among newer antidepressants is difficult, given that all of them showed more or less similar efficacy and good tolerability. Nevertheless, individual patient preferences related to adverse effect profiles and cost of treatment, as well as adjusting the regimen appropriately, may provide the best approach. If a single drug fails, combined treatment with antidepressants having different modes of action may improve treatment efficacy. However, with such approach, the increased risk of interactions should be considered.

It is clear that there are substantial limitations in current antidepressant pharmacotherapy and there is a need for new therapeutic approaches. Advances in understanding the neurobiology of depression have opened up a new era of investigations with novel therapeutic approaches and compounds based on new mechanisms of action. Today, research is focused on a variety of targets such as the L-arginine-nitric oxide-cyclic guanosine monophosphate pathway, the endocannabinoid system, sigma-1 receptors, melatonin, 5-HT_6 and 5-HT_7 receptor antagonists, β_3 adrenergic antagonists, vasopressin receptor antagonists, and NK_2 tachykinin receptor antagonists. Although the potential efficacy of these agents remains to be established, the future of antidepressant treatment appears to be promising.

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Disclosure

The authors report no conflict of interest in this work.

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