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Individualized Pharmacological Treatment of Depressive Disorders State of the Art and Recent Developments

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Abstract

During the past decade a variety of promising new compounds were launched onto the market. These are influencing serotonergic, noradrenergic, and dopaminergic neurotransmission, and interact with melatonergic and serotonergic receptor systems.

The main advantages of all newer drugs are a broadening of the spectrum of available treatments, better safety and tolerability profiles in comparison to older compounds and the focus on specific symptoms of depression including insomnia and cognitive disturbances.

Still unresolved issues are the relatively high non-response rate during the first weeks of antidepressant treatments, a latency of sometimes several weeks until clinical improvement and remission can be achieved, and a variety of possible side effects also present during treatment with modern compounds.

The pharmacological treatment of depression of medium to high severity is mandatory. In case of severe depression dually acting antidepressants may be of advantage. Besides the severity of the disease subtypes of depression, specific symptoms as well as age and comorbidity of the patients may play a role influencing the treatment outcome. The treatment providing the highest response probability, the best safety and tolerability and the best effects on the individual symptoms of depression should be preferred in individualized treatment plans.

This narrative review summarizes the actual knowledge of the comparative efficacy and individual effectiveness together with safety and tolerability profiles of all to date approved antidepressant classes according to their pharmacodynamic principles of action. A detailed description of the latest approvals of antidepressants is included.

The study of new treatment options is of major importance to provide better strategies for the clinical management of depression in the future, and is thus also of great socio-economic importance.

Keywords: Antidepressants; Dopamine; Efficacy; Melatonin; MAO-inhibitors; Noradrenalin; Serotonin reuptake inhibition; Tolerability; Tricyclic antidepressants

Introduction

According to information from the World Health Organization (WHO) depressive disorders are of outstanding socio-economic and health-economic importance as they are the psychiatric disorders that most frequently cause psychosocial disability. By virtue of the Global Burden of Disease report 2004 they were the number one cause for moderate and severe disability independent of socio demographic factors with increasing importance in the projection to the year 2030 [1]. The multifactorial genesis of depressive disorders requires a multimodal and individualized treatment. Typical symptoms of depression are summarized in Table 1.

Category of depressive symptoms	Symptoms
Affective symptoms	Depressed mood Anhedonia Anxiety
Psychomotor disturbances	Retardation Agitation Loss of energy and activity
Disturbances of cognition and memory	Feelings of guilt Feelings of worthlessness Mood-congruent and -incongruent delusions Concentration deficits Memory deficits
Psychovegetative disturbances and somatic complaints	Insomnia Diurnal changes Loss of appetite and weight Sexual dysfunction Constipation Pain syndromes Hypertonia Tachycardia

Table 1: Symptomatology of depressive disorders, modified according ICD-10 and DSM-5 [203-205].

The severity of symptoms, diagnostic subtypes and presence of specific symptoms, as well as age and psychiatric or somatic comorbidity play a role influencing the course of illness and choice of treatment. The treatment which provides the best tolerability together with the highest likelihood of response should be preferred in treatment plans and algorithms. Treatment of depressive disorders mostly consists of a combination therapy, determined by the current clinical features. The main constituents of a multimodal antidepressant therapy are pharmacotherapy, psychotherapy using established therapeutic techniques, and social support. Less severe forms of depression

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require at least watchful and active waiting [2,3], but patients may also experience benefit from pharmacological treatments [4,5]. Moderate and severe depression usually requires pharmacotherapy, or electroconvulsive therapy (ECT) in treatment resistant illness, if available in combination with psychotherapy and complementary treatments such as social support, occupational therapy and exercise training.

Therefore the detection of antidepressant acting chemical agents represents an important milestone for the treatment of depressive disorders. In the 1950s for the first time the antidepressant properties of the tuberculostatic Monoamine Oxidase Inhibitor (MAOI) iproniazide and the Trizyclic Antidepressant (TCA) imipramine were described [6]. Initially the latter was misleadingly considered as an antipsychotic medication. Currently available antidepressants are classified according to their chemical structure and their pharmacodynamic mode of action (Table 2). Available classes are tri- and tetracyclic antidepressants, which represent predominantly a group of non-selective combined serotonin- and/or noradrenalin-reuptake inhibitors, selective and non-selective inhibitors of monoamine oxidase, selective serotonin reuptake inhibitors (SSRI), selective Noradrenaline Reuptake Inhibitors (NARI), and antidepressants with a dual mode of action such as selective Serotonin and Noradrenalin Reuptake Inhibitors (SNRI), Noradrenergic and Specific Serotonergic Antidepressants (NaSSA), Dopamine and Noradrenaline Reuptake Inhibitors (DNRI) [7], and a melatonergic MT_1/MT_2 receptor agonist with $5HT_{2C}$ receptor antagonistic properties [8]. Current investigational compounds include dopaminergic, Serotonergic and Noradrenergic Triple Reuptake Inhibitors (SNDRI) and glutamatergic mechanisms [9].

Especially newer antidepressants, which not only enhance serotonergic and noradrenergic neurotransmission, but also influence more selectively the dopamine, glutamate, and the melatonin receptor systems, have the advantage of a better tolerability profile when compared to older compounds. Predominantly, they exert less anti-cholinergic side effects, but attention hast to be paid to other new side effect profiles. The use of antidepressants with anti-histaminergic properties, e.g. NaSSA or TCA may cause daytime sleepiness and an increase of appetite [10]. In case of NARI treatment tremor, tachycardia and restlessness, in case of SSRI treatment loss of appetite and body weight, nausea, headache and sexual dysfunction are important. Especially the latter are reported only rarely without systematic assessment. Table 3 is summarizing the assumed mechanisms and the resulting side effect profiles.

High dropout rates due to such tolerability problems which limit the treatment adherence, may contribute to a high rate of nonresponse: approximately 30% of the treated patients are not responding sufficiently to the treatment [11]. Besides a high nonresponse rate the US STAR*D study found also low *remission rates* even after multiple treatment trials [12,13].

A further problem in the pharmacotherapy of depression is the latency of up to several weeks until symptoms are alleviated [14], though a faster onset of response has been described for newer dual acting compounds such as mirtazapine [15-17]and venlafaxine [17,18]. Only ECT [19,20] and sleep deprivation [21] are established treatment options producing more rapid antidepressant effects. Recently also experimental treatments with the N-Methyl-D-aspartate (NMDA) antagonist ketamine [22,23] and new Deep Brain Stimulation (DBS) techniques [24] have shown promising results indicating a faster improvement of severely depressed mood in difficult to treat patients.

Antidepressant	Class	Dosing recommendations according to the manufacturers	
		Starting dose (mg)	Maintenance treatment (mg/day)
agomelatine	MT	25	25–50
amitriptyline	TCA	25–75	150–300
amitriptylinoxide	TCA	30–60	180–300
amoxapine[1]	TCA	50	100–400
bupropion	DNRI	100	200–300
citalopram	SSRI	20	20–40
clomipramine	TCA	25–50	100–250
desipramine	TCA	25–75	100–300
dibenzepine[1]	TCA	120–180	240–720
dosulepin/ dothiepin	TCA	75	75–150
doxepine	TCA	25–75	150–300
duloxetine	SNRI	60	60–120
escitalopram	SSRI	5–10	10–20
fluoxetine	SSRI	20	20–80
fluvoxamine	SSRI	50–100	100–300
imipramine	TCA	25–75	150–300
isocarboxacid[1]	MAOI	20	20–60
lofepramine[1]	TCA	70	140–210
maprotiline	TCA	25–75	150–225
melitracen[1]	TCA	20	20–30
mianserine	TCA / NaSSA	30	60–120
milnacipran[1]	SNRI	50	100–200
mirtazapine	NaSSA	15	30–45
moclobemide	RIMA	150–300	300–600
nefazodone[1]	SMA	100	300–600
nortriptyline	TCA	25–50	75–300
paroxetine	SSRI	20	20–60
phenelzin[1]	MAOI	15	30–90
protriptylin[1]	TCA	10	20–60
reboxetine	NARI	4	8–12
selegiline[1]	MAOBI	orally: 30 transdermal application: 6	orally: 30–60 transdermal application: 6–12
sertraline	SSRI	50	50–200
tianeptine[1]	GM	37.5	37.5
tranylcypromine[1]	MAOI	10	20–40
trazodone	SMA	50–100	200–600
trimipramine	TCA	25–50	150–400
venlafaxine	SNRI	75	75–375
viloxazine[1]	NARI	100	200–500
vortioxetine[1]	SSRI, MMA	5	20

[1]Not all antidepressants are marketed and available in all countries

Abbreviations: DNRI = dopamine and noradrenaline reuptake inhibitor; GM = glutamatergic modulator; MAOI = irreversible inhibitor of monoamine oxidase A and B; MAOBI = inhibitor of monoamine oxidase B; MMA = multi-modal antidepressant; MT = melatonergic antidepressant, melatonin 1 and melatonin 2 receptor agonist and $5HT_{2c}$ antagonist; NARI = selective noradrenaline (norepinephrine) reuptake inhibitor; NaSSA = noradrenergic and specific serotonergic antidepressant; RIMA = reversible inhibitor of monoamine oxidase A; SMA = serotonin modulating antidepressant; SNRI = selective serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tri- or tetracyclic antidepressant

Table 2: Available antidepressants and recommended dosing strategies (mg per day) (modified according to [7] and [206]).

The aim of the present narrative review was to provide a combination of the actual evidence based knowledge of efficacy and effectiveness of specific groups of antidepressants subdivided according to their assumed pharmacodynamic mode of action. Special attention should be paid to antidepressants being approved by American and European health authorities recently.

Receptors or neurotransmitters	Mode of action	Typical side effects (receptor)[1]	Typical antidepressants
M_1 receptor	antimuscarinic/ anticholinergic	dry mouth accommodation disturbances constipation micturation disturbances worsening of angle-closure glaucoma hyperhidrosis cognitive disturbances delirium cardiac arrhythmias	TCA paroxetine
H_1 receptor	anti-histaminergic	sedation drowsiness daytime tiredness increased appetite weight gain metabolic syndrome	TCA mirtazapine
$\alpha_{1/2}$-receptor	antiadrenergic	hypotension	TCA
NA transporter	noradrenaline reuptake inhibition / noradrenergic effects	tremor hyperhidrosis dry mouth tachycardia restlessness sleep disturbances hypertonia	NARI SNRI DNRI
5HT transporter blockade / 5HT receptor agonism	serotonin-reuptake inhibition / serotonergic effects	headache ($5HT_{1D}$) restlessness, agitation, akathisia ($5HT_2$) anxiety, panic ($5HT_2$) decreased appetite, weight reduction ($5HT_2$) sleep disturbances ($5HT_2$) sexual dysfunction ($5HT_2$) nausea ($5HT_3$) diarrhea ($5HT_4$) nausea ($5HT_3$) restless legs syndrome ($5HT_{2c}$) serotonin syndrome (all 5HT receptors; predominantly in combination) lack of emotion SIADH enhanced bleeding risk	SSRI SNRI serotonergic TCA NaSSA
MT1, MT2	melatonin agonism	tiredness	agomelatine

[1]The sorting order according to a grading from common and less serious to more serious but rare side effects

Table 3: Common side effects of antidepressants. Side effect profiles and pharmacodynamic modes of action (modified according to [7]).

Antidepressant properties of neuromodulatory techniques such as Transcranial Magnetic Stimulation (TMS), Magneto-Convulsive Therapy (MKT), Vagus Nerve Stimulation (VNS), or Deep Brain Stimulation (DBS) are not reviewed here. Due to increasing scientific evidence for the clinical effectiveness the use of psychotherapy is suggested as a mandatory supplementation in most routine treatments of depressed patients. Especially Cognitive Behavioral Therapy (CBT), Interpersonal Psychotherapy (IPT), and the cognitive behavioral analysis system of psychotherapy (CBASP) are used successfully in the treatment of more chronic forms of depression. The different treatment approaches in psychotherapy regarding depression are beyond the scope of this review, therefore they are not evaluated here.

Our targets are evidence based and clinically useful recommendations for an individualized pharmacological treatment of depression. This may contribute to better safety and tolerability enhancing treatment adherence. Consequently, the clinical effectiveness of antidepressant acute treatment should result in an optimized outcome.

Treatment Goals

Traditionally the treatment of depressive disorders can be subdivided in acute, maintenance, and in prophylactic treatment [25,26]. First treatment goal is the rapid improvement and response to treatment. Response is defined usually as a 50% reduction of depressive symptoms, determined usually with the Hamilton Rating Scale for Depression (HRSD, HAM-D) [27] or the Montgomery-Åsberg Depression Rating Scale (MADRS) [28]. The clinical management of depressive disorders usually exceeds these criteria used predominantly in clinical trials. To define the goal of clinical remission divergent criteria are in use [29], finally the complete absence of depressive symptoms without the presence of diagnostic criteria of depresssion is the clear intention of antidepressant treatment. In clinical trials e.g. a HRSD total score below 8 is used as remission criterion. This is recognized as prerequisite for complete restoration of the premorbid social and occupational performance levels of the patients in the medium and long term. Besides the complete health recovery further goals of the antidepressant treatment are the prevention of further depressive episodes and a good quality of life [30].

The individual goals of clinical treatments can be reached frequently using a sequential and/or combined treatment including also pharmacological augmentation strategies, psychotherapy, social support, and complementary treatments. The effects in clinical trials can be shown better in responder analyses than using the usually small mean differences in the HRDS or MADRS scale [31]. Here differences between active drug and placebo of about 20% can be reached. This corresponds to a number needed to treat (NNT) of 5, which means that five patients have to be treated to reach a benefit in one patient. A NNT

of 5 corresponds to medium to strong effectiveness which is similar to many treatments used frequently in internal medicine [32].

From a patients´ viewpoint the most important criteria for remission are the restoration of optimism, self-confidence and the premorbid positive self-evaluation, which includes a completely restored level of functioning in all aspects of daily living [33]. This is especially true because only after full remission the relapse risk can be considered as reduced and acceptable [34,35].

Initializing treatment with antidepressants

The first line antidepressant treatment should exert the best possible clinical effectiveness, which can be assumed for most of the available and approved antidepressants to be on similar levels [36] comparing mean differences in clinical trials together with the best safety and tolerability profile. Exceptions from this principle can be found in some head-to-head comparisons, meta-analyses [37] and in comparisons of specific patient subgroups [7,32].

Due to a usually very good tolerability, pharmacological treatments of first choice include SSRIs, agomelatine, dually acting selective antidepressants such as SNRI, NaSSA, DNRI, or also a RIMA. Economic pressure predominantly, but not exclusively in developing countries, still also facilitates the broader use of older antidepressants such as TCAs, especially those newer ones with lesser anticholinergic and antihistaminergic properties.

While antidepressant combinations and augmentation using atypical antipsychotics or lithium (and to a far lesser extend also thyroid hormone augmentation) are common strategies in more difficult to treat depression, the use of an irreversible MAOI due to the safety profile and the use of ECT due to high expenditure for the hospitals are limited to patients with higher grades of treatment resistant depression.

In case of complex symptoms which are not responding sufficiently or fast enough to monotherapeutic approaches with only one antidepressant, e.g. in psychotic depression, depression with pronounced suicidality, but also when agitation or insomnia are shaping the clinical picture, the early combination with antipsychotics, benzodiazepines or non-benzodiazepine hypnotics is indicated.

In the following, we are summarizing the clinical highlights of antidepressants available to date in Europe and the US (Table 2). For the evaluation predominantly randomized controlled trials (RCTs) and meta-analyses of data collected in the treatment of adults in the age of 18 up to 65 were used. Due to historical reasons we retain to the mixed classification using also the chemical structure of antidepressants (only TCA), but our main classification criteria are the pharmacodynamics principles of action which seem to have more clinical relevance. Actualized guidelines which contribute to the basis of this review can be found in the publications of Bauer et al. [38,39].

Classification of Antidepressants and Clinical Highlights

Selective serotonin reuptake inhibitors (SSRIs)

To date seven SSRIs are approved in Europe: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vortioxetine. Because the latter received the EMA approval and marketing authorization recently in December 2013 [40] it is described more in detail in the chapter dealing with new antidepressants. Despite the fact that the supposed pharmacodynamic modes of action of all SSRIs are similar and consequently also the efficacy seems to be comparable in clinical trials, the practical use of these substances shows clinically meaningful differences. Causes are pharmacodynamic properties beyond the inhibition of the serotonin transporter such as modulation of receptor activities, different interaction potentials, different half-lifes and consequently also different side effect profiles.

The comparative efficacy of SSRIs within the same group [41] and in comparison to other antidepressants [42,43] was reported to be similar. At the same time, the tolerability profile was favorable in comparison to TCA. The high selectivity and low interaction potential of citalopram [44], escitalopram [45], and sertraline [46] are noteworthy. Moreover, treatments of anxious depression using escitalopram [45], paroxetine [47], or fluvoxamine [48] were especially successful, while fluoxetine [49] and sertraline [46]showed good effects in atypical unipolar depression. The discussion about comparative efficacy was restarted after a multiple-treatments meta-analysis which used the method of both direct and also indirect comparisons of second-generation antidepressants [50]. Here advantages especially of escitalopram [51] and sertraline in terms of efficacy and tolerability were described. Also recent Cochrane reviews and meta-analyses re-evaluated efficacy and tolerability of SSRIs within and between antidepressant classes: citalopram was recognized as more effective than paroxetine (and NARI), but less effective than escitalopram [52]. Escitalopram was confirmed to be more effective than citalopram and fluoxetine [53]. Sertraline was more effective than fluoxetine, but less effective than NaSSA and DNRI; nevertheless tolerability was not only better than in TCA and NaSSA, but also in comparison to paroxetine [54]. Fluoxetine was more effective than the SNRI milnacipran, but less effective than venlafaxine from the same group, NaSSA, and within SSRIs sertraline [55]. No new findings about superiority or inferiority of fluvoxamine could be found [56]. The class comparison of NaSSA and SSRIs was partly contradictory: first an advantage of NaSSA was assumed [57], later only nominal differences without statistical significance [58], finally superiority to sertraline [54] were published.

Nevertheless, for specific subgroups of patients who are severely depressed and/or hospitalized, TCA, especially amitriptyline treatment seems to be more effective (but still less tolerable) in comparison to SSRIs [59,60].

In addition, the disadvantageous tolerability profile of the oldest SSRI paroxetine [54] which has the highest rate of anticholinergic side effects among SSRIs [47] has to be mentioned. Also noteworthy is the long half-life of fluoxetine of up to 4 days and its active metabolite norfluoxetine of up to 15 days which has to be considered in treatment plans [61]. It is of advantage in abruptly discontinued treatments due to a usually lower rate (but not complete absence) of discontinuation symptoms [62,63]. But it also may complicate changes in treatment regimes, especially in case of subsequent treatment with MAOI.

Serotonergic side effects of SSRIs [64] are mentioned above and summarized in Table 3. Rarely occurring side effects are a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) which can result in hyponatremia and generalized epileptic convulsions, which may be even prolonged in case of SSRI treatment [65]. Due to decreased platelet concentrations or a diminished platelet aggregation also an enhanced bleeding risk, especially during co-administration of other thrombocyte aggregation inhibitors such as aspirin, clopidogrel or similar medications may be an additional risk factor. The life threatening serotonin syndrome including disorientation, restlessness, myoclonus, hyperreflexia, and tremor fortunately is a rare event, but

may be provoked in case of overdose or pharmacokinetic interactions [66].

Clinical implications and recommendations:

- There is evidence for the best efficacy of escitalopram, citalopram and sertraline which are also the most selective and therefore best tolerable SSRIs. They are a good choice for first line treatments.
- SSRIs are treatments of choice in anxious and atypical depression.
- Most SSRIs (with the exception of anti-cholinergic effects of paroxetine) have favorable tolerability profiles.
- The long half-life of (nor) fluoxetine has to be considered in case of treatment changes.

Selective noradrenalin reuptake inhibitor (NARI)

Up to now reboxetine is the only NARI approved in Europe. It is not FDA approved for the treatment of depression in the US. First non-inferiority in comparison to the TCA imipramine [67] and the SSRI sertraline [68] were described. In a direct comparison to fluoxetine [69] and to citalopram in patients suffering from post-stroke depression including a marked loss of drive [70] it showed superiority, in comparison to TCA in the treatment of melancholic depression [71]inferiority was published. Meta-analyses comparing multiple treatments demonstrated both similarity [51] and clear inferiority [37] in comparison to other modern antidepressants resulting temporarily in the withdrawal from reimbursement lists of some health insurances.

The safety and tolerability profile is good [72] and superior in comparison to TCA. Sexual dysfunction [73], nervousness, anxiety and gastrointestinal side effects [71] are less frequent in reboxetine than in SSRI treatment. Typical side effects are tachycardia, dry mouth, hypertonia and a loss of weight. Due to α-receptor agonism micturition disturbances may occur even in the absence of anti-cholinergic effects. In this case the α_{1A}-receptor antagonist tamsulosin may be useful. Due to the approval of other NARIs such as atomoxetine for the treatment of attention deficit hyperactivity disorder (ADHD) and evidence also for the efficacy of reboxetine in this patient group [74] MDD with comorbid ADHD may be a specific indication for reboxetine.

Clinical implications and recommendations:

- Especially in case of intolerability of SSRIs due to serotonergic side effects a switch to reboxetine may be helpful.
- NARIs may be especially useful in patients with anergic depression and comorbid ADHD.

Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

Duloxetine and venlafaxine are approved by the EMA and the FDA, within Europe milnacipran is not available in all countries.

Even if the blockade of the noradrenaline transporter in lower dosages seems to be stronger after using duloxetine in comparison to venlafaxine [75], responder rates after the use of SNRIs were similar [76,77]. Duloxetine had similar efficacy in comparison to SSRIs and to venlafaxine, while it was inferior in terms of acceptability and tolerability [78]. It showed superiority in comparison to paroxetine [79], but also non-inferiority in comparison to paroxetine [80] and escitalopram [81]was published.

Venlafaxine was superior efficacious in comparison to SSRIs [82], similar response rates in comparison to sertraline [83] and fluoxetine [84] were reported. Direct comparison to escitalopram showed divergent results [85,86]. Meta-analyses showed superiority over fluoxetine [87] and considering remission rates also to paroxetine [76,82,88]. In comparison to the TCA imipramine milnacipran could not demonstrate any superiority [89] while venlafaxine was similar effective in comparison to the NaSSA mirtazapine [90].

The side effect profile was superior in comparison to TCA [76], but venlafaxine showed a higher risk for discontinuation syndrome and for hypertension in comparison to the SSRI sertraline [83]. In total, the tolerability of duloxetine seems to be better [76], but it caused also more side effects in comparison to the SSRI paroxetine [80]. Serotonergic side effects such as gastrointestinal symptoms and sexual dysfunction as well as noradrenergic side effects such as hypertonia are more frequent in the use of higher dosages [91] and immediate release preparations [92]. The safety of venlafaxine in case of overdose is better in comparison TCA, but worse in comparison to SSRIs [93].

Clinically important is the reduction of chronic (neuropathic) pain syndromes during duloxetine and venlafaxine treatments, because they are a frequent comorbid condition in depressive disorders [94-96]. Independent of the presence of depression, duloxetine is also approved in the treatment of chronic diabetic polyneuropathy [97].

Clinical implications and recommendations:

- Due to the excellent efficacy SNRIs are considered as the "gold-standard" of modern efficacious antidepressants, which are often used in comparative clinical trials and in clinical routine treatment.
- SNRIs are also used successfully in treatment resistant / difficult to treat depression.
- Duloxetine and venlafaxine can reduce not only symptoms of depression, but also ameliorate chronic pain.

Noradrenergic and specific serotonergic antidepressant / α-receptor blocker (NaSSA)

Mirtazapine and mianserine belong to the group of dually acting antidepressants enhancing both serotonergic and noradrenergic signaling. The blockade of α_2-adrenergic auto- and heteroreceptors increases both noradrenaline and serotonin release. In addition, in case of mirtazapine the $5HT_2$- and $5HT_3$-blockade prevents some of the serotonergic side effects [98].

Whereas mianserine and mirtazapine treatment showed no significant differences in comparison to TCA [99], mirtazapine had a faster onset of action [100] and was more effective than SSRIs [101-103]. In addition, mirtazapine was more effective than the SNRI venlafaxine [101,104]. In comparison to NARI or SNRI no faster onset of action could be detected [105,106].

Beneficial effects on sleep disturbances [107] are mediated by anti-histaminergic effects which are also responsible for the most common side effects such as initial dizziness and sedation together with increased appetite and weight gain [108]. Additional antinociceptive properties were shown in preclinical and clinical investigations [109-111], but data from larger RCTs are still lacking [112].

The safety and tolerability profile of NaSSA is better than that of TCAs [108] and similar to that of SSRIs [106]. Typical serotonergic side effects such as gastrointestinal complaints and sexual dysfunction

are registered rarely [113] due to the $5HT_2$- and $5HT_3$-blockade. The latter may be responsible for additional antiemetic effects [114]. Also beneficial effects in the treatment of neuropathic pain were reported [115]. Further clinically relevant side effects of mirtazapine are the induction or aggravation of a restless-legs syndrome (RLS) [116,117] and rarely also clinical relevant neutropenia [118]. For Mianserine also agranulocytosis was reported [119].

Clinical implications and recommendations:

- Due to good tolerability, rapid improvement and sleep inducing properties NaSSA are often used as first-line treatments of depression with insomnia and/or agitation.
- Combinations with SSRIs can enhance clinical effectiveness and reduce adverse events.
- The potential to reduce chronic pain is not as well documented as with SNRIs, but may be of additional clinical relevance.
- Metabolic changes or RLS may reduce the acceptability of the treatment.

Dopamine and noradrenaline reuptake inhibitor (DNRI)

Bupropion enhances the noradrenergic and dopaminergic neurotransmission by selectively inhibiting the reuptake of both monoamines into the synaptic cleft [120]. Similar to reboxetine it is one of the rare antidepressants not affecting relevantly the central nervous serotonin system [121]. It is approved for the treatment of depression and for smoking cessation.

Antidepressant efficacy of bupropion was similar to the TCAs amitriptyline [122], doxepine [123], and imipramine [124]. The same was true in comparison to the SSRIs fluoxetine [125], paroxetine [126], sertraline [127], and the SNRI venlafaxine [124,128]. Bupropion was especially effective in the treatment of depression accompanied by sleepiness and fatigue [129]. Also a failed study in Asian depressed patients which could not show any difference from placebo treatment which achieved similar response rates [130] has to be mentioned.

Due to missing anticholinergic and antihistaminergic side effects bupropion was better tolerated than TCAs [123], missing serotonergic effects are the cause for lower rates of both gastrointestinal side effects and sexual dysfunction in comparison to the SSRIs fluoxetine [125] and sertraline [127]. The induction of generalized seizures seems to be a rarely occurring safety issue [131]. Nevertheless, it has to be considered especially in patients with comorbid epilepsy or anorexia [132], and in case of accidental or intended overdose [133].

Clinical implications and recommendations:

- The DNRI bupropione is especially effective in treating anergic depression with fatigue.
- It is a useful alternative in patients suffering from clinically relevant serotonergic side effects.
- It may be supportive in depressed patients who need additional pharmacological support for smoking cessation.
- Risk factors for epileptic seizures should be considered.

Unselective serotonin and noradrenaline reuptake inhibitors / tricyclic antidepressants (TCAs)

TCAs usually are considered as a homogeneous pharmacological group even if they can be subdivided in a more clinically relevant way in medications with divergent pharmacodynamic modes of action. While most TCAs such as amitriptyline, desipramine, dosulepine, doxepine, imipramine, nortriptyline, and protriptyline are nonselective combined serotonin and noradrenalin reuptake inhibitors, clomipramine is influencing predominantly serotonergic, maprotiline noradrenergic and trimipramine dopaminergic neurotransmission. In case of tianeptine which is influencing the cortical serotonin transporter [134], also neuroprotective effects are discussed [135].

As described above, a better efficacy of some TCAs in comparison to SSRIs in severely depressed hospitalized patients were described [59,60]. Only one randomized study in elderly patients showed inferiority of tianeptine in comparison to the SSRI fluoxetine [136].Also evidence for a better efficacy of TCAs in elderly patients in comparison to SSRIs was reported [137]. Usually RCTs demonstrated similar efficacy of TCAs and SSRIs in the treatment of depression [138]. Even evidence for efficacy of a low dose TCA treatment was reported [139].

Nevertheless, TCAs were inferior to monoamine oxidase inhibitors (MAOIs) and SSRIs in the treatment of depression with atypical features (e.g. increased appetite, hypersomnia, leaden paralysis / heavy limbs, enhanced interpersonal rejection sensitivity) [140].

For the treatment of chronic neuropathic pain predominantly serotonergic/noradrenergic acting TCAs [96], especially amitriptyline [141], were administered, but meanwhile also SNRIs [96,142] and NaSSA [115] are used for this indication.

Factors limiting TCA treatment of depression are usually anticholinergic and antihistaminergic side effects [7] summarized in Table 3 more in detail. These represent not only specific medical risks for the treated patients, but limit also compliance, adherence and therefore the response probability during antidepressant treatment. In addition, the toxicity of TCA in case of overdose due to suicidal acts is higher in comparison to other antidepressants [143]. Here especially the cardiotoxicity with QTc interval prolongation and enhanced risks for arrhythmias has to be considered, whereas these risks are lower in some TCAs, e.g. desipramine or tianeptine [144].

Clinical implications and recommendations:

- Important treatment option especially in case of severe depression.
- Dependent on availability and economic pressure TCAs are most frequently second line treatments.
- Amitriptyline is on the WHO´s list of essential drugs.
- Beneficial in case of (comorbid) neuropathic pain syndromes.
- Higher risk for adverse events and higher toxicity has to be considered.

Monoamine oxidase inhibitors (MAOI, RIMA, MAOBI)

Irreversible inhibitors of the monoamine oxidase A and B (MAOI) such as tranylcypromine require specific safety precautions and are not available in some countries and restricted to second-line treatment recommendations in others. Less restrictive is the use of the selective and reversible monoamine oxidase A inhibitor (RIMA) moclobemide up to 900 mg/d [145] or the monoamine oxidase B inhibitor (MAOBI) selegiline up to 6 mg/24 h (which up to now has no EMA approval for the treatment of depression). Here especially after the administration of low dosages no dietary restrictions are required [7].

No efficacy differences between irreversible MAOIs and TCAs

could be found predominantly in outpatients [146]. Also no significant difference to an SNRI/NaSSA combination treatment was reported [147]. Retrospective studies showed good effectiveness in treatment resistant [148], in atypical [140], and in anergic depression [149]. The RIMA moclobemide showed a lower effect size in comparison to tranylcypromine in severe depression which can be compensated by dose escalation [150]. No differences to SSRIs and TCAs were found. The MAOBI selegiline showed moderate, but significant antidepressant effects administered as a transdermal patch [151].

MAOIs are recommended in case of specific features of the depressive disorder such as atypical features or difficult to treat and treatment resistant depression. Otherwise, due to safety and tolerability issues they are considered as second line antidepressants [152]. The same is true for ultra-high dose escalating strategies in case of severe treatment resistant depression [153].

Due to the irreversible inhibition of the monoamine oxidase during MAOI treatment and at least two weeks after treatment cessation no combinations with other serotonergic medication [154]is allowed and dietary restrictions including low tyramine diet are important during this time to prevent hypertensive crisis with the danger of cerebral stroke. In case of switching from the RIMA moclobemide to another medication a 3 days waiting period is usually sufficient [7].

Similar safety issues including waiting times according to the half-life of the administered medications are important in case of switching from other serotonergic medication to MAOIs to prevent potentially lethal serotonin syndromes. Patients should wait at least 5 half lifes of the previous medication (usually 5-7 days, in case of fluoxetine 5 weeks) before taking MAOIs [7]. The side effect profile of MAOIs includes usually hypotonia, in case of dietary errors hypertensive crisis. In case of high dose treatment and after rapid cessation a delirium may occur. In addition, dopaminergic effects of MAOIs and amphetamine like effects of degradation products may produce a withdrawal syndrome after immediate cessation [155].

Clinical implications and recommendations:

- Irreversible MAOIs are important second-line treatments of treatment resistant depression.
- MAOIs may be especially effective in atypical and anergic depression.
- Low-dose RIMA or MAOBI treatment does not require dietary restrictions.
- MAOI treatment includes the risk of severe side effects such as hypertensive crisis and stroke, delirium, and withdrawal syndromes.

Recently Approved Antidepressants

Melatonin MT_1 and MT_2 agonist and $5HT_{2c}$ antagonist – agomelatine

The pharmacodynamic mechanisms of agomelatine combine MT_1 and MT_2 agonism with $5HT_{2c}$-antagonism. Melatonin is secreted by the pineal gland and acts as the endogenous circadian rhythm oscillator by stimulating melatonergic receptors in the Suprachiasmatic Nucleus (SCN) in the hypothalamus. A variety of preclinical investigations demonstrated that melatonergic effects can be enhanced by agomelatine effects on the SCN and other brain regions without modifying melatonin concentrations [156]. Because circadian rhythms are known to be altered in depression [157] it has been postulated that an advance in circadian rhythms by influencing MT receptors and a blockade of oversensitive $5HT_{2c}$ receptors [158] which is not suppressing, but normalizing the signaling at $5HT_{2c}$ sites [156], contribute to antidepressant effects [159]. In addition, beneficial effects on sleep disturbances without direct antihistaminergic sedation and without changing of the sleep profile, e.g. without rapid eye movement suppression, could be demonstrated [160,161].

In a recent Cochrane review including both, published and unpublished data of 13 studies in more than 4400 patients, the efficacy of agomelatine was compared to the SSRIs escitalopram, fluoxetine, paroxetine, sertraline, and to the SNRI venlafaxine [162]. With respect to both primary outcome variables overall response and remission rates no significant differences could be detected, but minimal nonsignificant superiority was reported for paroxetine, non-significant inferiority for sertraline and escitalopram. A similar nonsignificant nominal inferiority was reported for venlafaxine. The only significant differences could be detected concerning side effect profiles: Agomelatine showed significantly fewer side effect rates and was therefore better tolerated than paroxetine and venlafaxine, also fewer agomelatine treated patients dropped out of the trials due to side effects compared to both, sertraline and venlafaxine [162]. Similarly, a recent review including 20 published and unpublished trials in 7460 participants confirmed a better antidepressant effectiveness of Agomelatine in comparison to placebo and an overall similar effectiveness in comparison to standard antidepressants, but clear superiority over sertraline [163].

Prior RCTs demonstrated comparable efficacy with respect to response and remission in comparison to the SSRIs escitalopram [164], paroxetine [165], and the SNRI venlafaxine [166]. In comparison to sertraline superior effects of agomelatine on depressive symptoms were reported [167]. In comparison to fluoxetine a clinically relevant similar antidepressant efficacy in an Asian patient population was described [168]. Moreover, superiority of agomelatine over fluoxetine in severely depressed outpatients was reported [169]. Superiority concerning efficacy over SSRIs and SNRIs including escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine was supported also by a meta-analysis and two pooled analyses [170-172].

As described before the tolerability profile was good and most side effects were as frequent as during placebo treatment [165]. Especially a lower rate of sexual dysfunction [173], predominantly in comparison to serotonergic substances such as the SNRI venlafaxine [166], and a lower risk for adverse events after rapid discontinuation in comparison to paroxetine [174] have to be mentioned. Recent reports about agomelatine induced hepatotoxicity, e.g. in case reports [175,176] and other spontaneous reports [177] indicated higher risk in patients with pre-existing liver disease. A further non-interventional study could detect lower rates of elevated liver enzymes above 3 fold normal levels in 0.2 to 0.4% of the study population [178] in comparison to the rates detected in clinical trials. A recent review shows that several antidepressants (iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, tianeptine) including agomelatine are associated with greater risks of hepatotoxicity [179]. Therefore the EMA recommendation not to use agomelatine in patients with pre-existing liver diseases nor in patients whose level of transaminases are more than three times the normal level seems to be beneficial for the treated patients [180]. To enhance treatment safety, the measurement of liver enzymes is recommended at the beginning of the treatment and after dose escalation in intervals of 3, 6, 12 and 24 weeks (and in case of clinical need). It should be repeated within 48

hours in case of enzyme level elevations [181].

Clinical implications and recommendations:

- The combination of both good effectiveness and tolerability supports the use of agomelatine as a first line treatment.
- Agomelatine is the first sleep inducing antidepressant without antihistaminergic side effects.
- Especially patients sensitive to serotonergic side effects show good acceptability and adherence to agomelatine treatment.
- Regular determinations of liver enzymes enhance the treatment safety markedly.

Selective serotonin reuptake inhibitor with $5HT_{1A}$ agonistic and $5HT_{1B}$ partial agonistic properties, a multimodal antidepressant - vortioxetine

Because vortioxetine is not only affecting the serotonin transporter, but acts also as a $5HT_{1A}$ against, $5HT_{1B}$ partial agonist together with $5HT_{1D}$, $5HT_3$ and $5HT_7$ antagonistic properties, it is described as a multimodal antidepressant [182]. Multimodality was described precisely as the combination of actions at the G protein receptor ($5HT_{1A}$ and $5HT_{1B}$ partial agonism and $5HT_7$ antagonism) together with ion channel modifications ($5HT_3$ antagonism) in combination with neurotransmitter 5HT transporter blockade [183]. Data from rodent experiments show a resulting modulation in several neurotransmitters including serotonin, noradrenalin, and dopamine systems [184,185]. It is postulated that these effects contribute not only to the antidepressant efficacy, but also to further specific properties including anxiolytic, analgesic and cognitive enhancing properties [186,187].

Vortioxetine was approved by the FDA in September and by the EMA in December 2013 for the treatment of major depressive disorder [188].

The results of clinical trials in patients suffering from MDD show a total of three negative studies investigating the treatment of predominantly lower doses of vortioxetine over 6-8 weeks in comparison to placebo: In the first study 2.5 and 15 mg [191] could [189], in the second 5 mg [190] and in the third 10 and 15mg [191] could not separate significantly from placebo treatment. In summary, there seems to be a higher probability of insufficient efficacy in lower dosages of vortioxetine. Moreover, one failed study of vortioxetine 2.5, 5 and 10 mg with duloxetine 60 mg as an active reference showed no differentiation from placebo in primary treatment outcome variables neither in the duloxetine, nor in the vortioxetine groups [192].

In contrast, 10 mg vortioxetine treatment for 8 weeks resulted in a significant better outcome in comparison to placebo [193]. The same was true in a study comparing 10 and 20 mg vortioxetine with placebo for 8 weeks [194]. Also in comparison to placebo and an active drug a significant better amelioration of depressive symptoms in comparison to placebo could be demonstrated: After 6 weeks of treatment 5 and 10 mg of vortioxetine as well as 225 mg of venlafaxine were superior to placebo treatment [195]. The same was true for an 8 weeks treatment with 15 or 20 mg vortioxetine and 60mg duloxetine in comparison to placebo: both antidepressants were significantly superior to placebo and the response in the duloxetine group validated the study [196]. Finally, a further comparison of 15 and 20 mg vortioxetine and 60 mg duloxetine treatment over 8 weeks separated duloxetine and 20 mg per day vortioxetine from placebo whereas no statistically significant difference could be shown after 15 mg vortioxetine [197]. Even if it´s not exactly in the scope of this review, it should be mentioned, that both 5 mg vortioxetine and 60 mg duloxetine could be differentiated significantly from placebo after 8 weeks of treatment in a selection of elderly patients (mean >70 years). Interestingly besides the symptoms of depression, also cognition tests including speed of processing, verbal learning and memory variables improved markedly in the vortioxetine treated group [198].

A recent review summarizes the effectiveness of vortioxetine in the treatment of MDD with advantages over other antidepressants as active comparators with respect of tolerability, but not with respect of overall effectiveness [199].

Further positive results were reported from a placebo-controlled relapse prevention study [200]. In addition, two open long term studies without placebo control demonstrated clinical effectiveness over a 12 month lasting treatment [201-205].

Up to now the data from the above mentioned clinical trials showed an excellent tolerability profile of vortioxetine with predominantly serotonergic side effects. In comparison to the active SNRI comparators venlafaxine and duloxetine vortioxetine caused a lower rate of side effects and consecutive study drop outs.

Clinical implications and recommendations:

- Vortioxetine broadens the spectrum of efficacious and well tolerated treatment options for MDD.
- The multimodal mechanism of action contributes to the good tolerability profile.
- In addition, it may help to ameliorate cognitive impairment in depression resulting in better psychosocial reintegration.

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