SEROTONIN, NOREPINEPHRIN, DOPAMINE – COMBINING MEDICATION AGAINST DEPRESSION

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A monotherapy or a combination of antidepressants that affect all three monoamines serotonin, dopamine and norepinephrine together have led to some positive results in cases of treatment-resistant depression, while some promising substances that could be used as monotherapy are still in the early stages of development. In any case, it is important to weigh off the potential benefits of antidepressant combinations, while being mindful of the potential adverse effects associated with antidepressant combinations, particularly if they have a synergistic effect in a neurotransmitter system. As there is still not enough data to provide clear guidance to the clinician, one may have to work together with a well-informed patient to try out different options cautiously and gradually.

Keywords: serotonin, norepinephrine, dopamine, antidepressants, major depressive disorder, medication, treatment, psychiatry

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Introduction

Antidepressants that act on two or more amine neurotransmitters may confer higher remission rates when first-line agents affecting a single neurotransmitter have failed. However, there are also more potential side effects, which requires that the clinician diligently weighs off the benefits and costs of the antidepressant treatment. The more we understand about the interactions of the different neurotransmitter systems and subsystems, and their effects on clinical parameters, the easier it will be to individually tailor an antidepressant therapy to a particular constellation of symptoms in a patient.

The Neurotransmitter Triad

Dysfunction in the monoamine systems of serotonin, norepinephrine and dopamine may causally be related to major depressive disorder. The monoamine hypothesis based on the deficiency of one or several monoamines is commonly evoked to explain the physiopathology of depression. This hypothesis initially based on noradrenalin and serotonin deficiency has been extended to dopamine. Monoamine depletion studies [1] have investigated the direct effects of monoamines on mood. Serotonin, norepinephrine or dopamine depletion did not decrease mood in healthy controls, while it slightly lowered mood in healthy controls with a family history of major depressive disorder. (Ruhé, Mason, & Schene, 2007) However, it needs to be remembered that this only shows a correlation and does not necessarily reflect causation.

[1] For example, tryptophan depletion or para-chlorophenylalanine deplete serotonin, acute phenylalanine/tyrosine depletion or alpha-methyl-para-tyrosine deplete norepinephrine/dopamine.

Extensive studies showed that monoaminergic neurotransmission that involves serotonin, norepinephrine and dopamine exerts major influence on brain circuits concerned by the regulation of mood, reactivity to psychological stress, self-control, motivation, drive, and cognitive performance. Antidepressants targeting monoamines influence the functioning of these of these neuronal networks, notably in limbic and frontocortical areas, and evidence has been provided that this action plays a key role in their therapeutic efficacy. (Hamon & Blier, 2013) Indeed, at least some of functional changes detected by functional magnetic resonance imaging in emotion- and cognitive-related circuits such as the one involving limbic-cortical-striatal-pallidal-thalamic connections in depressed patients can be reversed by monoamine-targeted antidepressants. (Hamon & Blier, 2013)

Interconnected Systems

Practically all the neural networks on one side and the neurotransmitter systems on the other are interconnected, if only indirectly, because the optimal use of information dictates it. (Haverkampf, 2018a) In particular, serotonin systems were shown to exert negative influence on norepinephrine and dopamine systems through 5-HT2A and 5-HT2C receptor- mediated mechanisms, respectively. On the other hand, complex positive and negative influences of norepinephrine system on serotonin neurotransmission are mediated through α1- and α2-adrenergic receptors, respectively. (Hamon & Blier, 2013)

The interconnectedness plays a role in several combination approaches and could also explain some of the antidepressant effectiveness of substances that affect primarily the dopaminergic systems, such as the dopamine and norepinephrine reuptake inhibitor bupropion and the atypical antipsychotics, the latter as augmentation strategies in combination with and SSRI, for example. Understanding more about the connection points not only between the neurotransmitter systems, but also along receptors subtypes for example, can help to design more effective treatment combinations with lower side effects.

Analysis of the monoamine networks and their dysfunctions suggest that drugs with selective or multiple modes of action on dopamine and norepinephrine may have robust therapeutic effects. Understanding the mode of action of drugs targeting norepinephrine and dopamine, for example, can improve their utilization in monotherapy and in combination with other compounds particularly the SSRIs. The elucidation of such relationships can help design new treatment strategies for major depression, especially the treatment-resistant type. (El Mansari et al., 2010)

Treatment-Resistant Depression

Treatment-resistant depression is a major health concern. More than 40% of patients treated for major depressive disorder with an appropriate antidepressant dose for an adequate duration fail to respond. Further, approximately half of adults with major depressive disorder fail to achieve sustained remission despite various medication trials. Unfortunately, many healthcare providers see a depression as something that is difficult to treat. This is, however, untrue. With the tools we have available, truly treatment-resistant cases are rare. This, of course, does not only include several stages of medication, which have been diagrammed in several treatment algorithms, but also psychotherapeutic approaches, which should always be combined with a pharmacological approach (Haverkampf, 2018b, 2018c).

There are several treatment algorithms and recommendations for an evidence-based sequence of pharmacological treatment choices in the face of treatment resistance. Often, they tend to agree on an SSRI as a first-line monotherapy. If this does not lead to a substantial remission, the next step would be an increase in the dose of the initial antidepressant. Thereafter, the next steps can include switching to a different SSRI or SNRI within the same group, followed by a switch to an agent from a different group, before combining two antidepressants with different mechanisms of action, such as bupropion and an SSRI or mirtazapine and venlafaxine, adding non-antidepressant medication, such as lithium or certain atypical antipsychotics (olanzapine, aripiprazole, or quetiapine) to the antidepressant. One may also add a natural product, such as l-methylfolate or s-adenosylmethionine (SAMe) (Preston & Shelton, 2013), although the risks may frequently outweigh the potential benefits.

Augmentation with Antidepressant vs Non-Antidepressant

Most patients with major depressive disorder fail to remit after initial antidepressant treatment trials. The results of the Study of Treatment Alternatives to Relieve Depression (STAR*D) trial suggest that most patients require antidepressant combination and augmentation treatments. Antidepressant combination strategies are widely used by clinicians for the management of treatment-resistant depression, albeit with scant empirical support, even for the most widely used combinations. Augmentation treatments, such as

adjunctive lithium, thyroid hormone or atypical antipsychotics, often have stronger evidence from well-designed randomized controlled trials to support efficacy. (Carvalho, Macêdo, Hyphantis, & Mc Intyre, 2013) It appears that many clinicians feel more comfortable using only antidepressants in combination. However, this is probably based on the assumption that an antidepressant is made for the treatment of depression, while a non-antidepressant is not. This is, of course, incorrect. The more we learn about how substances affect the different neurotransmitter systems and neuronal networks, the more the boundaries between traditional antidepressants blur. One should also remember that antidepressants themselves are frequently used for other indications apart from depression, such as anxiety and, mostly off-label, insomnia.

There are major differences among treatment algorithms for depression regarding the timing of the augmentation, the additional substances used and the roles of MAO inhibitors. (Spijker & Nolen, 2010) For example, the Dutch algorithm referred to by the authors consists of five subsequent steps if there is no sufficient response:

1. Monotherapy with an antidepressant
2. Switching the monotherapy after 4–10 weeks
3. Augmentation with lithium
4. Switching to a monoamine oxidase inhibitor (MAOI)
5. Electroconvulsive therapy (ECT)

What seems to be missing from this list are, however, the augmentation with second-generation antipsychotics and, possibly with lower empirical support, antidepressant combinations, that many clinicians in daily practice would prefer to MAO inhibitors, with their generally higher risks for serious adverse effects and required alimentary precautions, and ECT.

Dopamine Agonist and SSRI

Greater activation of dopaminergic and serotonergic neurotransmission leaves out norepinephrine from the monoamine triad, but there has been some research into that combination, which is interesting also

because of the connections between the dopaminergic and serotonergic systems, which seem to play a role in depression and anxiety. However, Franco-Chaves and colleagues examined the efficacy and safety of combination therapy with pramipexole, a dopamine agonist and the SSRI escitalopram in major depression. The outcome of the pilot study with 39 patients with DSM-IV major depressive disorder who had failed to respond to a standard antidepressant treatment was that the combination was not more effective than either agent alone, did not produce a more rapid onset of antidepressant action, and appeared to be less well tolerated. (Franco-Chaves et al., 2013)

DNRI and SSRI

An example of a serotonergic, noradrenergic and dopaminergic strategy is the combination of the dopamine norepinephrine reuptake inhibitor (DNRI) bupropion with an SSRI. Controlled and open-label studies support the effectiveness of bupropion in reversing antidepressant-associated sexual dysfunction, whereas open trials suggest that combination treatment with bupropion and an SSRI or SNRI is effective for the treatment of MDD in patients who are refractory to the SSRI, SNRI, or bupropion alone. (Zisook, Rush, Haight, Clines, & Rockett, 2006) Data suggests that, although not an approved indication, the combination of bupropion and either an SSRI or an SNRI is generally well tolerated, can boost antidepressant response, and can reduce SSRI or SNRI-associated sexual side effects. (Zisook et al., 2006) Bupropion is frequently added in the US to SSRIs or SNRIs to combat the sexual dysfunction caused by the serotonergic medication. (Dunner, 2014)

In a naturalistic, open-label study, patients with major depression who had not responded to at least 6 weeks of treatment with citalopram or bupropion were treated by a combination of the two substances (Lam, 2004). Results indicated that the combination was superior to either monotherapy in these treatment-resistant depressed patients, and that it was well tolerated without a greater side effect burden. However, it may also be that the noradrenergic effect in the dopamine norepinephrine reuptake inhibitor plays a significant role. So has another study indicated that in depressed patients who partially responded to lithium augmentation of an SSRI, the further addition of a noradrenergic antidepressant, bupropion or desipramine, substantially improved their symptoms (Moret, 2005)

There is also data on the potential usefulness of the combination of bupropion and an SSRI form animal models. The forced swimming test is an animal model used to predict the antidepressant activity of drugs. The antidepressant-enhancing effects of bupropion in this model bupropion have indicated that bupropion may enhance the efficacy of the therapeutic effect of SSRIs and SNRIs but not the therapeutic effect of an NRI. (Prica, Hascoet, & Bourin, 2008)

DNRI and SNRI

Using a retrospective chart review Papakostas and colleagues identified patients with major depressive disorder who had not experienced full remission of symptoms following an adequate trial of either duloxetine (n=3) or bupropion (n=7), and who then received the combination of duloxetine and bupropion. Three (30%) patients were remitters at follow-up, and six (60%) were responders who did not achieve full symptom remission. (Papakostas et al., 2006). However, Lai presents a case of treatment-resistant depression with full recovery where a combination of mirtazapine and bupropion was used after a failed response to combined mirtazapine and duloxetine treatment. (Lai, 2009)

Patients with a DSM-IV diagnosis of major depression with atypical features and a history of treatment resistance, were evaluated in a preliminary six-week study. By week 6, only five (21.7%) patients receiving duloxetine and placebo vs. six (26.1%) patients on the bupropion combination achieved response. No significant difference in final HAM-D scores between the two groups was observed between those patients achieving response. The presence of a higher number of atypical features significantly predicted non-response. In those patients receiving bupropion, treatment-emergent adverse events leading to withdrawal were more common among those receiving lower doses of the combination drug, and no life-threating dangers were noted. (Fornaro et al., 2014)

In an animal model, the co-administration of venlafaxine with bupropion resulted in a dramatic increase in extracellular dopamine, and this effect was significantly greater than that seen with bupropion alone. In the rat frontal cortex, norepinephrine was elevated by bupropion alone and venlafaxine alone, relative to the control animals. The combination of bupropion and venlafaxine resulted in a marked elevation of NA. (Hudson, Lalies, & Silverstone, 2012)

Menezes and colleagues investigated the effects of paroxetine, venlafaxine and bupropion alone or in the combinations of bupropion with either the SSRI paroxetine or the SNRI venlafaxine on spatial and affective memory tasks in adult rats. Behavioral tests included measures of spatial memory (radial-arm maze), aversive memory (passive avoidance), open field and forced swimming tests. In the spatial memory test, venlafaxine with or without bupropion impaired learning, while short-term memory was impaired by paroxetine, bupropion and their combination. Venlafaxine and bupropion improved it as compared to bupropion. Paroxetin impaired long-term memory. Venlafaxine and bupropion alone impaired STM and long-term fear memory, whilst paroxetine and bupropion or venlafaxine with bupropion did not induce significant alterations. (Menezes et al., 2018)

DNRI vs Antipsychotic

Both, bupropion and the antipsychotics have effects on the dopamine neurotransmission system, the former mostly in increasing its information transmission, while the latter also has inhibitory effects. The antidepressant effectiveness of combinations of these compounds with SSRIs is probably also to a part at least to the interconnections between the serotonergic and dopaminergic systems. Among adjunctive treatments, the addition of atypical antipsychotics has probably the best efficacy and the earliest onset of response. The initial studies of augmentation were done with risperidone; in the United States both quetiapine and aripiprazole are approved for augmentation treatment in depression. (Dunner, 2014) These antipsychotic medications tend to result in about a 50% response rate within about two weeks of adding them to antidepressants. (Dunner, 2014)

Both aripiprazole and bupropion appear to help reduce sexual dysfunction and fatigue in patients with major depressive disorder. In a randomized, prospective, open-label study between aripiprazole and bupropion augmentation with 103 patients both treatments significantly improved depressive symptoms without causing serious adverse events. However, significant differences in remission rates between the two groups were evident at week 6, favouring aripiprazole over bupropion. There were no significant differences in adverse sexual events, extrapyramidal symptoms, or akathisia between the two groups. (Cheon et al., 2017)

MAO Inhibitors

Already in 1964, a reviewer observed that "clinical use of monoamine oxidase (MAO) inhibitors has been characterized by recurrent cycles of enthusiastic reports of therapeutic successes, the occurrence of serious adverse reactions and consequent withdrawal of the original inhibitor, and the synthesis of new compounds. The first cycle began in 1957 when iproniazid (Marsilid), introduced initially for the treatment of tuberculosis, was found to have pronounced euphoric effects that led to its use in the treatment of psychological depression." (Goldberg, 1964) Today, the MAOIs are still included among MDD treatment recommendations in internationally recognized guidelines. The introduction of reversible, or selective, MAOIs offers treatment options that reduce safety concerns regarding diet and medication interactions associated with conventional MAOIs, and dietary instructions are less restrictive. (Zajecka & Zajecka, 2014)

The enzyme monoamine oxidase breaks down, and thereby lowers the levels of the neurotransmitters norepinephrine, serotonin and dopamine. MAOIs prevent this from happening, thereby increasing their levels. In spite of their demonstrated strong effectiveness against depression and conditions such as social anxiety, the utilization of monoamine oxidase inhibitors (MAOIs) for the treatment of depression in clinical practice today is relatively low due to their lower safety and greater potential interactions with other medication as compared to the SSRIs, for example. Their potentiation of cardiovascular effects of dietary amines ("cheese effect") is well known to anyone who has studied medicine over the last half century.

A number of reversible MAO-A inhibitors which are devoid of cheese effect have been described in the literature, but only one, moclobemide, is currently in clinical use. (Finberg & Rabey, 2016) For these reasons, MAOIs are not recommended to be prescribed along with other antidepressants or certain prescription or non-prescription drugs. Although, in some smaller studies combinations of MAO inhibitors and other antidepressants have been tried.

Further combining the MAO inhibitors with other antidepressants has for a long time been considered taboo because of the potentially strong synergistic push on the neurotransmitter systems, which could lead to dangerous consequences. However, in a review of published cases and a retrospective case series of 29 adults with a combination of a MAO inhibitor and another antidepressant or stimulant, Thomas and

colleagues conclude that although risks of combination treatment certainly exist with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, or clomipramine, the current literature supports cautious use of combining MAOIs with other antidepressants in patients with treatment-resistant depression who have failed multiple treatment modalities. (Thomas, Shin, McInnis, & Bostwick, 2015) A small trial is also mentioned by the authors in which about one in five patients with treatment resistant depression was significantly helped by such a combination. However, due to the significant risks of this approach, it should be reserved to those clinicians with significant experience in such combinations and only used in patients where everything else has failed, including MAO inhibitor monotherapy, as a very last resort in the face of a severe depression.

Side Effects

The drugs in a combination have their own potential side effects which can be more than additive due to the use of a combination. Thus, monotherapy is usually preferred, if possible. By themselves, due to their specificity of action and receptor profile, newer antidepressants carry a relatively low risk for pharmacodynamic drug interactions, at least as compared with first-generation antidepressants, such as MAO inhibitors and tricyclic antidepressants. (Spina, Trifirò, & Caraci, 2012) Two examples of possible combination interactions are given in the following. However, many more exist, and some among them can even be potentially lethal.

Cytochrome 450

All new antidepressants are extensively metabolized in the liver by cytochrome P450 (CYP 450) isoenzymes, and parallel use of inhibitors or inducers of the CYP 450 isoenzymes involved in the biotransformation of specific antidepressants may cause changes in their plasma concentrations. However, due to their relatively wide margin of safety, the consequences of such kinetic modifications are usually not clinically relevant. (Spina et al., 2012) Duloxetine and bupropion are moderate inhibitors of CYP2D6. Therefore, potentially harmful drug interactions may occur when they are co-administered

with substrates of these isoforms, especially compounds with a narrow therapeutic index. (Spina et al., 2012)

QTc Prolongation

The occurrence of QTc prolongation (with increased risk of torsade de pointes) has been reported for several antidepressants, including the newer ones, as well as many other drugs. Stella and colleagues investigated in their review of controlled clinical studies and case reports the association between newer generation antidepressants and the occurrence of cardiovascular adverse events and electrocardiogram (ECG) abnormalities. Aging, higher dosages of antidepressants, drug interaction, and pre-existing cardiovascular comorbidities were found as risk factors for the cardiovascular and ECG abnormalities. (Stella, Loureiro, Pais, Canineu, & Forlenza, 2017)

Conclusion

A combined effect on the three monoamines serotonin, norepinephrine and dopamine seems to bestow advantages, particularly in treatment-resistant cases. However, at the same time an increased incidence of side effects and a wider spectrum of them is the potential cost of greater effectiveness. Combinations that pair an SSRI or SNRI with a dissimilar antidepressant, such as bupropion or mirtazapine, are widely used for patients who have not responded to trials of first- or second-line antidepressant monotherapies.

Other than the monotherapies targeting the three monoamines, such as the MAO inhibitors, there is still is no strong evidence that even the most widely used combinations have particular merit, while alternatives with a better demonstrated efficacy exist. Also, it may take full therapeutic doses of both drugs across a typically adequate duration of exposure to achieve the desired effects of combined treatment. (Thase, 2013) Other issues are that we know little about how individual cognitive functions and symptoms of depression may be affected separately by the antidepressants and antidepressant combinations. There is thus a need for the design of adequately powered randomized controlled trials to provide a clearer evidence base for the widely employed clinical practice of combining antidepressants,

such as the one consisting of bupropion with a serotonergic antidepressant. (Carvalho et al., 2013) Until then one should exercise caution, while at the same time not denying a patient treatment options that help in the fight against a condition that causes more suffering than most others.

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