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## The Monoamine Oxidase Inhibitor Isocarboxazid is a Relevant Treatment Option in Treatment-Resistant Depression-Experience-Based Strategies in Danish Psychiatry

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### Abstract

The clinical use of monoamine oxidase inhibitors (MAOIs) like isocarboxazid nowadays is most often seen with treatment resistant depression, which is in accordance with the registered indication of the National Health Service of Denmark. The clinical use, however, early became restricted and today it covers only a minority of the market for antidepressants.

The aim of the present paper is to give a short overview of the clinical efficacy, to review mechanisms of action and metabolism of MAOIs, and to discuss how the side effects and interactions with these drugs may be avoided.

A number of clinical trials have documented that MAOIs are effective antidepressants in major depression, including in patients with melancholic syndrome. In Denmark the combined use of nortriptyline with isocarboxazid as add-on treatment for more than 30 years has proved to be safe and efficient. MAOIs must never be combined with SSRIs and serotonergic TCAs.

The normal dose of isocarboxazid may cause oedema, which can be treated with a supplement of 100-200 mg pyridoxine (vitamin B6). Isocarboxazid is metabolized by hydrolysis by the liver enzyme carboxylesterase. In contrast to most other antidepressants, the liver enzyme CYP2D6 is not involved in the metabolism of isocarboxazid, which means that it can be used in normal dose for all patients.

Treatment with isocarboxazid needs precautions with a number of other drugs and the necessity to avoid certain foodstuffs containing excessive amounts of tyramine. Danish patients being treated with isocarboxazid are recommended to carry along a simple instruction, containing general advice for health personal and a list of foods to avoid. Treatment with isocarboxazid is considered to be a relevant option in treatment-resistant depression and we are today much better prepared than we were many years ago to use the drug in our rational pharmacotherapy.

**Keywords:** Denmark; Genetic polymorphism; Isocarboxazid; Monoamine oxidase inhibitor; Treatment-resistant depression; Tryptophan; Tyramine; Vitamin B6

### Introduction

Isocarboxazid is the only one of the classical monoamine oxidase inhibitors (MAOIs), which is marketed in Denmark. In 1980 a paper on long-term treatment of depression with isocarboxazid suggested that treatment with monoamine oxidase inhibitors like isocarboxazid should not be left untried in the case of therapy-resistant depression [1]. This is in accordance with the registered indication of the National Health Service of Denmark, however, nowadays worded as treatment-resistant depression (TRD) [2]. Also in the late 1970 a paper stated that "the use of MAOIs has been underutilized and a resurgence of interest in the MAOIs is timely" [3]. Meanwhile, in the era of newer antidepressants from the 1980 isocarboxazid was never routinely used. In 2013 the market share of isocarboxazid in Denmark accounted for only 262.000 defined daily doses (DDD's) (0.2%), which corresponds to about 400 patients. In comparison 151.601.000 DDD's (93.9%) were prescribed for use of SSRI (selective serotonin reuptake inhibitor) antidepressants and other newer antidepressants [4].

The reasons for this development were the risk of side effects with isocarboxazid, as well as the potential interactions with other drugs and certain foods, but also ignorance about how isocarboxazid is metabolized in the liver.

The concept of TRD was introduced in 1974 and accordingly TRD is

normally defined as an insufficient response to two different antidepressants from two separate pharmacological classes [5]. It is generally estimated that at least 20% of the depressive patient population is suffering from TRD, thus TRD is one of our major health challenges [6,7].

As in the late 1970 'ies we still estimate the use of MAOIs including isocarboxazid to be underutilized [3]. Therefore considering the great number of patients with TRD we have found it worthwhile to revisit the drug.

The aims of the present review is to give a brief overview of the clinical efficacy of isocarboxazid, including in combination with other antidepressants, to discuss the mechanisms of action and metabolism, to give an account of the adverse effects and interactions and to explain how they may be counteracted.

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## The Clinical Efficacy of Isocarboxazid in Monotherapy and in Combination with Other Antidepressants

The clinical efficacy of isocarboxazid was never well established in randomized controlled trials [1,8] and for many years the clinical specificity of monoamine oxidase inhibitors in so-called atypical depression was intensely, however, inconclusively studied [9-11].

In 1991 atypical depression usually characterized by “increased duration of sleep, weight gain, blames of others, intrusive character deviation and irritability” was also studied with the selective and reversible monoamine oxidase inhibitor moclobemide, however, no interaction between treatment and atypical or not atypical depression was found [11]. A re-analysis of the moclobemide data, however, pointed at a clinical specificity of moclobemide with atypical depression [12]. More important, in the 1991-study, moclobemide was found to be slightly inferior to clomipramine and isocarboxazid [11]. Likewise in a prospective clinical practice study from 2001 electroconvulsive therapy (ECT), tricyclic antidepressants (TCA) and classical monoamine inhibitors were found to be more effective than SSRIs, reversible monoamine oxidase inhibitors and antipsychotic drugs in depression with melancholic syndrome [13].

Combined use of tricyclic antidepressants and monoamine oxidase inhibitors is controversial. In combination treatment amitriptyline often was considered as the optimal tricyclic antidepressant with various irreversible monoamine oxidase inhibitors like tranylcypromine, phenelzine and isocarboxazid [14-16]. Generally it is strongly recommended to use the monoamine oxidase inhibitor as an add-on treatment to the tricyclic antidepressant and never to combine with TCAs in the serotonergic end of the TCA spectrum, like clomipramine [2]. Though also later studies used amitriptyline in combination with MAOIs [17,18], for more than 30 years the active main metabolite of amitriptyline, nortriptyline was preferred with isocarboxazid in Denmark [1].

Isocarboxazid must never be combined with SSRIs and most new antidepressants. However, a study on combined isocarboxazid-mianserin treatment in 60 patients with endogenous depression showed that the two antidepressants effectively and safely could be combined from start of treatment [19].

A 56 year old female patient was admitted to hospital after a serious suicidal attempt. For years she had been treated with SSRIs without sufficient effect. She recovered with a series of ECT treatments, however, shortly afterwards relapsed. Treatment with nortriptyline was initiated. As she did not obtain full remission, isocarboxazid 30 mg, starting with 10 mg, was added to the 150 mg nortriptyline and she soon recovered. Since then she had for more than 8 years been completely well without depressive symptoms, and following advice concerning foodstuff and other drugs without observed or reported adverse effects.

A 60 year old man was seen in the outpatient clinic with a serious major depression with suicidal ideation, which had gradually developed after he lost his job. Treatment with nortriptyline 150 mg was initiated, however, never resulted in full remission. Add-on treatment with lithium or quetiapine was without effect. Instead treatment with isocarboxazid was added gradually. At an add-on dose of 40 mg the depression had completely remitted, however, a dose of 20 mg was preferred, as the higher dose resulted in sexual dysfunction. On the latter add-on dose he was nearly without depressive symptoms and continued the combination therapy for years, also after he was back on the labour market again.

## Mechanisms of Action and How Isocarboxazid is Metabolised

The MAOIs are divided into two main categories, hydrazine derivatives like isocarboxazid and phenelzine and non-hydrazine derivatives like tranylcypromine [3,20]. They are irreversible MAOIs, which means that new enzymes have to be synthesized before it is safe to change antidepressive treatment from isocarboxazid to an alternative antidepressant. This may take about two weeks. It has been suggested that a clinical response corresponds with at least 80% inhibition of the monoamine oxidases, though it was never fully studied in clinical practice. Nevertheless a clinical response depends on a daily dose above a certain threshold [20].

Furthermore they are classified in type A and type B MAOIs according to substrate specificity in the mammalian brain. Isocarboxazid is a type A MAOI, which inhibit the degradation of serotonin, noradrenalin and dopamin, and relevant for the discussion of diet restrictions also tyramin.

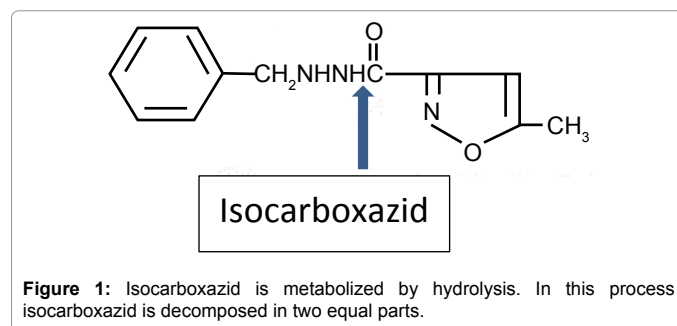
Isocarboxazid is metabolized by hydrolysis in the liver to inactive metabolites (Figure 1). The liver enzyme carboxylesterase is the principal cause of the metabolism [21].

In contrast to most other antidepressants, among these SSRIs and TCAs the liver enzyme CYP2D6 is not involved in the metabolism. This means that isocarboxazid can be used in normal dosage also in case of genetic determined polymorphism with a defect CYP2D6 enzyme system. The number of persons in Denmark who are metabolising most antidepressants and other psychopharmaceutical drugs too slow are above 7% [22].

### Adverse Effects

Isocarboxazid is normally well tolerated and in accordance with the literature and a recent Danish update the drug shows few side-effects. This applies also for the effect on the liver function, however, dizziness, headache, orthostatic hypotension and minor anticholinergic side effects may occur [2,14]. Sexual dysfunction has often been listed as one of the major problems of treatment with MAOIs, however, sexual complaints are difficult to validate, as loss of libido often is associated with depression [23]. Dose reduction may relieve the sexual dysfunction as the clinical case story above describes.

Clinical use of isocarboxazid may be associated with the development of oedema around the ankles, hands, fingers, stomach and eyes. If severe, this adverse event may necessitate discontinuation of treatment. Clinical experience has found that pyridoxine (vitamin B6) supplement counteracts the tendency to develop oedema during treatment with some MAOIs, including isocarboxazid [24,25]. Probably hydrazine derivatives like isocarboxazid react with pyridoxine



	Advice
Dietary prescriptions	Avoid matured cheese, overripe grapes and pickled herrings. Moderate amounts of red wine and white is tolerated. Eat only fresh foodstuffs, do not experiment with exotic meals.
To physicians and dentists	Guidelines for local anaesthetic, analgesic and other medical treatment.
Interaction with subsequent hypertension	I.v. injection with 50 mg labetalol one or more times.

**Table 1:** Patient instructions with advice for patients and health care staff.

to form a complex which inhibits pyridoxal kinase. This prevents the activation of pyridoxine to pyridoxal 5'-phosphate (PLP), thereby inhibiting numerous enzymatic reactions. Thus in a pilot study it has been shown that a supplement of pyridoxine in a daily dose of 100-200 mg significantly may reduce the oedemas [25].

### Interactions with Pharmaceutical Drugs and Foodstuffs

With the MAOIs simultaneous use of a number of drugs is contraindicated. This applies first of all for direct and indirect acting sympathomimetics like adrenalin, noradrenalin, ephedrine, amphetamine, methylphenidate, and others. This includes as well many asthma drugs, stimulants, certain cough and cold remedies and local anaesthetics with a vessel-constricting agent added. Also methadone should be omitted, as it inhibits the serotonin reuptake, and concomitant use of SSRIs is contraindicated because of risk of developing a serotonergic syndrome [2,20,26].

From the early 1960'ies it was observed that hypertensive episodes during treatment with MAOIs occurred with tyramine containing foodstuffs. Tyramine is formed from tyrosine in the process of maturing (cheese and pickled herrings), fermentation and putrefaction. All kind of cheese is in a stage of maturing, especially blue cheese, and only very fresh cheese contains very little tyramine [20,27]

The early MAOI diets recommended were unnecessarily restrictive. In fact, very few foods have sufficient tyramine content to approach the threshold of a serious hypertensive reaction [28]. A high-tyramine meal, however, is sufficient to increase blood pressure critically, when a substantial part of the monoamine oxidase has been inhibited. It may take only 8-10 mg of dietary tyramine to increase blood pressure when the monoamine oxidase is irreversibly "knocked out" by high doses of an MAOI [29]. In other words the interaction is dose dependent of as well the amount of tyramine as of the dose of isocarboxazid.

The content of tyramine has been analysed in a number of European foods and menus and revealed overall considerably lower contents of tyramine than reported previously [30]. In accordance with these measurements a Canadian study from 2013 included on the list of foods to be avoided, all matured cheese, fermented or dry sausage, improperly stored meat or pickled herrings, broad bean pods, all on-tap beer, sauerkraut, marmite concentrated yeast extract and soy sauce. On the other hand the same study allowed all fresh cheese products, all fresh packed or processed meat, fish and poultry products, and wine in modest quantities [31]. The Danish agent has prepared an isocarboxazid foodstuff instruction in Danish, which corresponds with the Canadian recommendations and the instructions from FDA from 2014 [32,33].

Patients being treated with MAOIs have generally been informed to avoid foodstuff containing high quantities of tryptophan because of risk of developing a serotonin syndrome [34]. Thus delirious reactions have been observed in patients on steady-state treatment with MAOIs when a dose of commercial L-tryptophan above 1 gram was added [35]. The content of various amino acids including racemic tryptophan has been measured in more than 100 food items. Overall the content of tryptophan was very low, for example 18 mg/100 mg in raw, peeled

bananas and 20 mg/100 g in cooked potatoes [36]. On a normal diet it is according to these measurements considered to be unlikely that toxic reactions to the combination of MAOIs and tryptophan may occur.

### Discussion

Depression is one of to-day's major health problems. Danish studies have shown that 3-4% of the population is suffering from moderate to severe depression [37] and furthermore the number of patients with atypical or treatment-resistant depression, who may potentially benefit from MAOIs, is substantial [31]. In Denmark it has thus been recommended that isocarboxazid ought to be included in the national guidelines for those patients who are resistant to conventional antidepressant treatment and ECT [2], which is in accordance with recent international reviews [28,31]. For unknown reasons isocarboxazid was not included in the latest revision of the Danish national guidelines from 2007 on the treatment of unipolar depression [2].

Treatment with MAOIs like isocarboxazid is an assignment for specialists; however, the understanding of the mechanisms of action and how the drug is metabolized make the treatment rational, easy and safe. For that purpose a simple instruction has been written, containing general advice (Table 1). Each single patient in treatment with isocarboxazid is recommended to carry along this instruction at any time including when travelling abroad. The instruction which is written in Danish has been translated into English and a number of European and Middle East languages.

For more than 30 years a procedure as mentioned above for using isocarboxazid in Denmark has been maintained. This may be the reason for the scarcity of drug and food interactions reported in Denmark and to the best knowledge of the authors none leading to lasting morbidity. Therefore isocarboxazid is still a relevant option in treatment-resistant depression and we are to-day much better prepared than we were many years ago to use the drug with rational skills.

Observational studies and more psychiatrists becoming familiar with the clinical use of the drug may be some of the future directions for the medication with isocarboxazid and for research to be recommended.

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