TDM monograph mirtazapine

Synonyms: Azamianserine

Summary

Indication:	Major Depression in Adults Off-label indications: Prophylactic treatment of chronic tension headaches, sleeping disorders (related to PTSS), sleeping disorders near the end of life, severe sleeping disorders in adolescents with a depression, itch in the palliative phase, anxiety in the palliative phase, akathisia (1-3) Indication TDM: Based on the current body of evidence routine TDM is not advised for mirtazapine. TDM of mirtazapine might be considered in case of side effects/toxicity or non-response to conventional dosages.
Sample material:	(coagulated) Serum or plasma (4-6)
Time of sampling:	At the end of the dosing interval (Trough level)
Storage conditions:	- 20 ºC
Interpretation:	Mirtazapine; 30-80 mcg/L (7)
Evidence level:	Total concentration: mirtazepine + N-desmethylmirtazapine: 50-300 mcg/L (8)

Contents

Introduction

Mirtazapine is indicated for the treatment of major depressive episodes in adults (11). It is a tetracyclic antidepressant derived from mianserine and falls within the group of the Noradrenergic and Specific Serotonergic Antidepressants (NaSSA). The major mechanism of action is the antagonism of the presynaptic α2-adrenergic receptors, additionally the 5HT2, 5HT3, histamine (H1) receptors are also antagonized by mirtazapine. Furthermore, mirtazapine also blocks the α1-adrenergic receptors in lesser amount (1-3,11). The commercial product of mirtazapine is a racemic mixture of the S(+) and R(-)enantiomers. The most important metabolite N-desmethylmirtazapine (NDM) is pharmacologically active, but less potent than mirtazapine and plays a non-significant role in clinical efficacy. A low of N-desmethylmirtazapine/mirtazapine ratio has been associated with side-effects (1-3,9,10,12). For more information on the pharmacology of mirtazapine see the section “pharmacodynamics” below.

Dosing guidelines

Depression

In adults with an episode of major depression mirtazapine is initially dosed at 15-30 mg/day, after a period of 2 to 4 weeks the dose may be titrated upward to 45 mg/day based on clinical effect and/or side effects. In case of an once daily regimen it recommended to administer the drug in the evening, while in a twice daily regimen it is advised to split the regimen in an uneven ratio with the higher dose in the evening (1-3,11). Initial effects of mirtazapine are usually observed after 1 to 2 weeks after start of therapy with a clinical response seen after 2 to 4 weeks with an adequate dose (3). In case of the first episode of major depression, the treatment should be continued for 6-12 months after the remission of depressive symptoms. In case of a recurring episode the treatment with mirtazapine should be continued for 12-24 months after clinical response (1-3,11). In the therapy of treatment-resistant depression mirtazapine is often used as additive antidepressant in case no sufficient response has been achieved with first-line antidepressants. It is often combined with selective serotonin re-uptake inhibitors (SSRI’s) and tricyclic antidepressants (TCA’s) as mirtazapine has an alternate mechanism of action (NaSSA) compared to the SSRI’s and TCA’s. The dosage of mirtazapine when combined with other antidepressants is often similar to monotherapy (13). To reduce possible symptoms of withdrawal is recommended to taper the dose of mirtazapine in case treatment is stopped (1,3).

Sleeping disorders

In addition, mirtazapine is used off-label to treat various sleep disorders (14-16). The clinical effect of mirtazapine on sleep disorders is usually seen at lower dosages (compared to the dosages for the treatment of depression) (14-16) The recommence starting dose of mirtazapine for the treatment of sleep disorders is 7,5-15 mg/day (1,14,17).

Dosing guidelines in children and adolescents

According to the manufacturer mirtazapine should not be used in children and adolescent below the age of 18 due to the absence of the evidence of clinical effect in clinical studies performed as part of the registration process and due to safety concerns (11). The Dutch Children's formulary recommends a starting dose of 7,5 mg daily with a maximum of 45 mg for adolescents between the age of 12 – 18 with the caveat that it should only be prescribed by a specialist in child and adolescent psychiatry in the lowest dose possible (18, 19).

Dosing guidelines in patients with altered pharmacokinetics

In case of decreased kidney function reduction of the dose of mirtazapine is not necessary (1,20). In patients with severe hepatic dysfunction a reduction in plasma clearance and an associated increase in half-life is observed which possibly warrants an upfront dose-reduction followed by titration based on clinical effect and side effects (21). There is currently no evidence supporting dose-adjustments in case of morbid obesity. In a limited number of clinical studies lower trough levels were observed as a result of possible lower resorption of the drug in patient who have undergone bariatric surgery (1,11,22-24).

Indications/Criteria for TDM

Currently, mirtazapine does not meet all the defined criteria for routine TDM:
1) a concentration-effect relationship for the indication depression has been observed in a number of clinical studies (9,10,25,26).
2) a large inter-individual variability in mirtazapine concentrations, the NDM concentrations and the NDM/mirtazapine ratio (with a respective CV of 38%, 33% and 36%). Additionally, on average higher levels were observed in elderly patients (> 65 years) compared to adolescents when treated with similar dosages (9,26). And in smokers lower concentrations of both the S(+) and R(-)enantiomers of mirtazapine were observed compared to non-smokers (27)
3) a high intra- interindividual variability (20% on multiple variables) (9)
4) a reliable assay for the determination of mirtazapine multiple matrices are available
However, there is currently no clinical evidence available suggesting that routine therapeutic drug monitoring of mirtazapine results in higher clinical efficacy.

Based on this information it is recommended to adjust the regimen of mirtazapine based on clinical effect / side effects. Therapeutic drug monitoring of mirtazapine can be useful in certain cases such as

- insufficient response to a conventional dose,
- to prevent / explain side effects or toxicity,
- in special subpopulation such as hepatic impairment or patients who have undergone bariatric surgery,
- a sudden decrease in clinical efficacy or sudden increase in side effects/toxicity and
- patients who started or stopped smoking (due to CYP1A2 induction).
- in case of possible inappropriate medication consumption (7)

Currently, the concentration of NDM is only clinically relevant when combined with a measurement of mirtazapine in relation to clinical efficacy or toxicity. Monitoring of NDM(+mirtazapine) compared to monitoring of mirtazapine only can provide additional information on possible sampling errors, to quantify / correct for drug-drug interactions, to identify abnormal metabolism (as result genetic variability in metabolizing genes) or monitoring of (non)adherence (7).

Reference values

Based on a review of the literature the **A**rbeits**g**emeinschaft für **N**europsychopharmakologie und **P**harmakopsychiatrie (AGNP) has concluded in their latest update of Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology that the therapeutic reference range for C_{trough} levels for mirtazapine is 30 – 80 mcg/L (7). The lower limit of this interval is mainly based on the studies from Grasmader et al, Myung et al, Reis et al and Shams et al (9,10,25,26). The upper limit of this concentration range is based on the upper border of the linearity of the kinetics of mirtazapine (15-80 mcg/L) (11,12).

In addition to the reference of the AGNP concerning only mirtazapine the reference for the total C_{trough} level of mirtazapine + NDM of 50 – 300 mcg/L is also used by laboratories which measure both mirtazapine and the NDM metabolite (8).

Efficacy

In a subgroup analysis of a clinical study (n=45 patient) performed by Grasmäder et al the percentage of response was significantly higher (77,3% vs. 23,8%) in patients with a C_{trough} above 30 mcg/L than patients with a C_{trough} below this threshold (25). A meta-analysis showed a relationship between concentration and clinical efficacy (measured with the Hamilton Depression Rating Scale) in a small population of 18 patients (28).

Relationship with occurrence of side effects & toxicity

Significant lower NDM concentrations and lower NDM/mirtazapine ratios have been observed in patients who experienced side effects as weight gain, dizziness and dry mouth compared to patient who did not experience these side effects (9,10). In the literature intoxications with mono-intoxications mirtazapine are generally described as mild. The clinical symptoms of a mono-intoxication with mirtazapine are usually somnolence/sleepiness, disorientation, hypo/hypertension and tachycardia (1-3,29-34). Lethal mono-intoxications with mirtazapine are rare, in literature only one case of a mono-intoxication has been described (35). Other lethal cases described involving mirtazapine concerned mix-intoxications (29-31. A concentration of 1000 mcg/L is often used by laboratories as toxic upper limit (originating from Clarcks), however multiple cases have been described where the patient presented with a concentration higher than 1000 mcg/L and survived (29,30). This toxic concentration of 1000 mcg/L likely originates from the upper limit of the linear curve in a HPLC/UV analysis (8).

Sampling & storage conditions

The provided references above relate to trough levels. Sampling should occur at the end of the dosing interval (12 hours in case of bidaily dosing and 24 hours in case of once daily dosing) or with an interval of

minimally 12 hours after the last dosing. After approximately one week on the same daily dose a steady state concentration is reached and sampling of mirtazapine can occur (4, 7, 27). Based on papers describing methods of analysis used in TDM of mirtazapine it is recommended to stored samples at -20 °C when the analysis does not occur directly. Mirtazapine in plasma is stable for one year at -20 °C and for 6 hours at room temperature (15-25°C) (4-6).

Additional information concerning the interpretation of results

In literature the serum concentration is sometimes related to the daily dose by using the “dose corrected concentration” (C/D). The C/D of mirtazapine and NDM was significantly higher in females compared to males (9,10). Inversely, this result reported by Reis et al and Shams et al implies that females require a lower dose compared to males to achieve the same serum concentration. A possible explanation for this phenomenon can be attributed to a lower body weight and resulting lower distribution of volume in the female patient in the cohorts of the published studies. Additionally, a higher NDM/mirtazapine ratio was observed in the females in these studies (9,10). The authors hypothesize that this can be explained by CYP3A4 being the most important route of metabolism of mirtazapine and higher levels of expression of CYP3A4 by females compared to males (9,10).

Background information [extended]

Pharmacodynamics

As mentioned in the introduction mirtazapine is a tetracylic antidepressant from the group of the NaSSA. The most important mechanism of action is the central antagonism of the presynaptic α2-adrenergic autoreceptors resulting in an increase of noradrenaline. The released noradrenaline binds to the post-synaptic α1-adrenergic receptors of serotonergic releasing nerves resulting in an increase of the release of serotonin. Additionally, the potent antagonism of the presynaptic inhibiting α2-adrenergic heteroreceptor results in a higher amount of serotonin in the synaptic cleft. The serotonergic effect of mirtazapine is then achieved by activation of the 5-HT_1 receptor by the higher amounts of secreted serotonin. Next to an indirect effect on the 5-HT_1 receptor mirtazapine directly antagonises the 5-HT_2 and the 5-HT_3 receptors (3, 36).

The registered mirtazapine product contains both the S(+) and R(-)enantiomers. The S(+)enantiomer is a more potent antagonist of the α2-adrenergic than the R(-)enantiomer, while the R(-)enantiomer is a stronger antagonist of the 5-HT_3 receptor. The clinical effect of mirtazapine on depression is attributed to the S(+)enantiomer, while the R(-)enantiomer is believed to prevent a number of side effects due to increased serotonin release, such as nausea, by antagonising the 5-HT_3 receptor. The R(-)enantiomer is also associated with the clinical effect of mirtazapine on heartrate and blood pressure. The metabolite NDM is thought to bind primarily to the 5-HT_1 receptor, however only 5-10% of the clinical effect of mirtazapine is attributed to NDM and compared to the parent drug this effect is considered not clinically relevant (3, 36).

Pharmacokinetics

Mirtazapine is absorbed quickly after oral dosing, with a Cmax after 1 to 3 hours and with a biological availability of 50%. The relatively low biological availability is the result of large first-pass metabolism.

Steady-state is reached after 4 days, except for elderly patient where steady-state is reached after 6 days (12).

Mirtazapine has a half-life of 20 to 40 hours. The major routes of biotransformation for mirtazapine are demethylation and oxidation followed by conjugation. CYP3A4 is responsible for the majority of the metabolism of mirtazapine resulting in NDM and mirtazapine-N-oxide. The metabolite 8-hydroxymirtazapine is formed by CYP2D6 and partially by CYP1A2. The metabolism of mirtazapine by CYP1A2 is of minor importance at low dosages, but the relative contribution of this enzyme increases when mirtazapine is given at higher dosages. A possible additional route of biotransformation involves the demethylation 8-OH-mirtazapine to 8-OH-NDM by CYP2B6, however this is not confirmed yet (see figure 1) (9).

The excretion of mirtazapine and its metabolites mainly occurs through urine (75%) and feces. Less than 4% of mirtazapine is excreted in its original form (12).

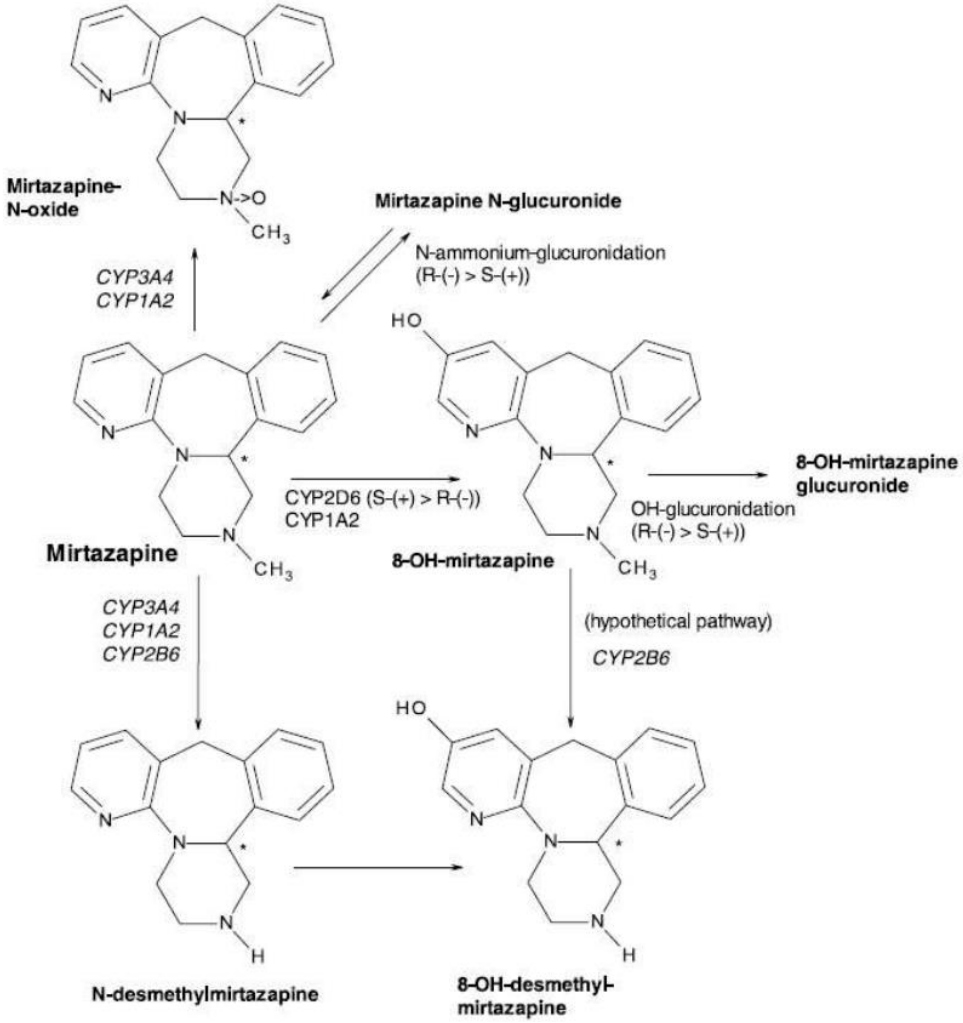

Figure 1: metabolism of mirtazapine (36)

Pharmacogenetics

In multiple clinical studies significantly higher trough concentrations of the S(+)enantiomer were found in patients with a *CYP2D6* genetic predicted phenotype of intermediate metabolizers (IM) and poor metabolizers (PM) compared to extensive/normal metabolizers (EM). Additionally, the concentration of the S(+)NDM metabolite was significantly higher in PM's than in EM's (27,36).
However, in a study of Sirot et al a significant effect of the *CYP2D6* genotype was only found on the NDM concentrations which did not translate to a significant change in clinical response or the occurrence in side effects (36). Furthermore, the Dutch Pharmacogenetics Working Group (DPWG) has concluded that aberrant *CYP2D6* genetic predicted phenotypes can lead to changes in concentrations, but does not lead to relevant clinical effects. For *CYP2C19* the DPWG has concluded that there is no effect of aberrant *CYP2C19* genetic predicted phenotypes on concentrations, clinical efficacy or the occurrence of side effect on mirtazapine treatment (1, 37). The clinical pharmacogenomics implementation consortium (CPIC) has no guideline on mirtazapine yet (38).
In their clinical study Sirot et al have found that the *CYP2B6 *6/*6* genotype was associated with a significant reduction in the score of the Hamilton Depression Rating Scale (HAMD) suggesting that mirtazapine has a higher efficacy in patients carrying the *CYP2B6 *6/*6* genotype (36). In the same study the group of Sirot confirmed that smokers have lower mean mirtazapine concentration than non-smokers. The higher exposure to polycyclic carbohydrates in cigarette smoke resulting in the higher induction of CYP1A2 in smokers was of such clinical significance that it masked the effect of the *CYP2D6* genotype, only in non-smokers aberrant genetic phenotypes of *CYP2D6* had a significant effect of mirtazapine concentrations (36).

Interactions

Strong inducers of CYP-enzymes such as bosentan, carbamazepine, fenobarbital, phenytoin, primidone, rifabutin, rifampicin and smoking can result in lower plasma concentrations of mirtazapine Inhibitors of CYP1A2 such as fluvoxamine can result in higher plasma concentrations of fluvoxamine (1, 39).

PK parameters

	F (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	**$t_{1/2}$** (h^{-1})	Protein binding	Tmax (h)	Ref.
General population	50%	455-945	1,5 – 5.0	20-40	85%	1-3	(1,12)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/ h^{-1}) **/ F**	Ref.
Hospitalized patients with a depression	$CL/F_i = CL/F \cdot e^{\eta_{CL}} \cdot [1 + CL/F1 \cdot (CYP2D6\text{-}2)]$ (IM = 1, EM = 2)	1.5	678	0.08	0.264	(40)

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Colophon

This guideline has been constituted by F. Lubberman, resident hospital pharmacy & I. van Berlo, hospital pharmacist under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

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Appendices

Not applicable

Revision

This guideline has been revised by dr. P.C.D (Paul) Bank, resident hospital pharmacy under supervision of dr. P.F.J. (Raphael) Schulte, psychiatrist, F.Ph. (Frouke) Mulder, hospital pharmacist and prof. dr. R.A.A. (Ron) Mathôt, hospital pharmacist & clinical pharmacologist.
The guidelines was updated based on most recent literature and translated to English.