Supplement to:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Atomoxetine Therapy

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Atomoxetine Therapy is published in full on the CPIC website (1). Relevant information will be reviewed periodically, and updated guidelines published online.

LITERATURE REVIEW

We searched the PubMed® database (1966 to August 2018) for the following keyword searches: 1) (cytochrome P450 2D6 or CYP2D6) AND (atomoxetine OR tomoxetine OR ly139603), and 2) atomoxetine AND (paroxetine OR fluoxetine). Using these search terms, 101 publications were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2D6* genotypes and metabolism of atomoxetine or atomoxetine-related adverse drug events or clinical outcomes or relevant drug-drug interactions. Non-English, review and commentary articles were excluded. Following application of these inclusion criteria, 24 publications were reviewed, scored, and included in the evidence table (**Supplemental Table S1**).

GENE: *CYP2D6*

Genetic Test Interpretation

CYP2D6 genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. *CYP2D6* haplotypes are assigned a star-allele (*) nomenclature to allow for the standardization of genetic polymorphism annotation (2, 3). A complete list of *CYP2D6* star-allele nomenclature along with the genetic variants that define each star-allele is available at PharmVar (https://www.pharmvar.org/). Information regarding *CYP2D6* haplotypes (star-alleles) is also available at PharmGKB (***CYP2D6* Allele Definition Table (1, 4))**. Knowing which SNPs or other genetic variants a particular test interrogates is important as the inclusion or exclusion of certain genetic variants in a pharmacogenetic test could affect the reported star-allele result.

Reference laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star-alleles (e.g., *CYP2D6*1/*10*, where an individual inherited a **1* allele and a **10* allele). Commonly reported *CYP2D6* star-alleles are categorized into functional groups (i.e.

normal function, decreased function, no function or increased function) based on the predicted activity of the encoded enzyme (***CYP2D6* Allele Definition Table (1, 4)**). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype. A *CYP2D6* genotype to phenotype translation table has been developed by CPIC and is updated on an ongoing basis on the CPIC website (1).

Calculating CYP2D6 Activity Score. Gaedigk *et al*. developed a scoring system to provide a uniform approach to assigning a predicted CYP2D6 phenotype (5). The activity value of each allele reported in the diplotype is added together to calculate the CYP2D6 activity score. For example, to calculate the activity score of a *CYP2D6*1/*17* diplotype, the activity value of **1* (activity value = 1) and the activity value of **17* (activity value = 0.5) are totaled to provide the CYP2D6 activity score of 1.5. Note that a value of 0.5 indicates decreased activity and not that the activity conveyed by an allele is half of that encoded by a normal function allele. An *in vitro* study has in fact demonstrated that *CYP2D6*17* is associated with lower atomoxetine metabolism (6). For this guideline, the CYP2D6 activity score is used to assign a predicted phenotype as follows: activity score of 0 = poor metabolizer, activity scores of 0.5 = intermediate metabolizer, activity scores ranging from 1.0-2.0 = normal metabolizer, and activity scores greater than 2 = ultrarapid metabolizer. Therefore, a pharmacogenetic test result of *CYP2D6*1/*17* would result in a CYP2D6 activity score of 1.5 and a predicted phenotype of normal metabolizer.

There has been a lack of consensus regarding whether patients with a CYP2D6 activity score of 1.0 should be assigned a normal or intermediate phenotype (7). Consequently, patients with genotypes giving rise to an activity score of 1.0 have been classified in the literature and reference laboratories as intermediate or normal metabolizers. The CPIC-initiated "genotype to phenotype translation standardization" working group is developing consensus recommendations for the field with the goal to harmonize and standardize the process of phenotype prediction from genotype data. Because this project is ongoing, this guideline uses the genotype to phenotype method used in previous CPIC guidelines with some modifications to account for the significantly decreased level of activity encoded by the *CYP2D6*10* allele (see main manuscript).

CYP2D6 Structural and Gene Copy Number Variants. Because *CYP2D6* is subject to copy number variation (gene duplications, multiplications, or deletions), clinical laboratories may report gene copy number if directly tested. Most patients will have a normal copy number of 2, with one gene copy inherited maternally and one gene copy inherited paternally. When two *CYP2D6* gene copies are present, the diplotype may be reported as follows: *CYP2D6*1/*1* or *CYP2D6 (*1/*1)2N*, where "2" represents the gene copy number. A copy number of "1" indicates the presence of a *CYP2D6* gene deletion (the patient possesses only one gene copy), and a copy number of "0" indicates both *CYP2D6* genes are deleted. *CYP2D6* gene deletions are indicated by the *CYP2D6*5* allele. A gene deletion that is present on one chromosome may be reported as follows: *CYP2D6*2/*5* or *CYP2D6 (*2/*2)1N*, where "1" represents gene copy number and the *CYP2D6*5* allele is inferred. Typically, clinical laboratories will report a homozygous gene deletion as *CYP2D6*5/*5* or *CYP2D6 (*5/*5)0N*.

A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "3" represents gene copy number. A clinical laboratory may not report an exact copy number, but rather indicate that additional copies of the *CYP2D6* gene are present (e.g., *CYP2D6*1/*2* duplication or *CYP2D6 (*1/*2)xN*). In instances where a duplication/multiplication is present, and the exact copy number is not reported, most patients will likely have a *CYP2D6* gene copy number of 3. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (8). Clinical laboratories typically do not determine which allele is duplicated, therefore when calculating CYP2D6 activity score the duplication must be considered for each allele reported in the diplotype (9). For example, a genotype result of *CYP2D6 (*1/*4)3N* indicates a patient has three copies of the *CYP2D6* gene, with either two copies of the *CYP2D6*1* allele and one copy of the *CYP2D6*4* allele, or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele. If the *CYP2D6*1* allele carries the duplication, the CYP2D6 activity score of this diplotype will be 2, whereas if the *CYP2D6*4* allele carries the duplication, the activity score will be 1. Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication/multiplication, a *CYP2D6 (*1/*10)xN* genotype, for example, can be consistent with a NM (normal metabolizer) phenotype (*CYP2D6*1/*10x2*; activity score of 2.0) or UM (ultrarapid metabolizer) phenotype (*CYP2D6*1x2/*10,* activity score of 2.5 or *CYP2D6*1x2/*10x2*; activity score of 3.0). As these examples illustrate, phenotype prediction will be more accurate if testing determines which allele

carries the duplication/multiplication and determines the number of gene copies present. Studies have been published describing the translation of *CYP2D6* genotypes into predicted phenotypes when gene duplications or multiplications are present (5, 9-12).

Note that a duplication may not be detected by copy number assays when paired with the *CYP2D6*5* allele (gene deletion). A *CYP2D6*2x2/*5* diplotype, for example, has a gene duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may be reported as *CYP2D6*2/*2*.

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (13, 14). The no function *CYP2D7-2D6* hybrid genes, collectively assigned as *CYP2D6*13* (15), may not be detected by a particular genotype test or gene copy number testing. In such cases the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a test that does not detect *CYP2D6*13* will report a *CYP2D6*1/*13* diplotype as *CYP2D6*1/*1*. Hybrid genes can also occur in duplication configurations and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (14, 16). For example, a *CYP2D6*1/*13+*2* diplotype (activity score = 2 predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* (activity score = 3 predicting ultrarapid metabolism).

Limitations of the Star (*) Nomenclature and Allele Assignments. The star (*) nomenclature has defined multiple subvariants for an allele (e.g., *CYP2D6*2* and **4*), but these are not distinguished by current testing. This is of no consequence for *CYP2D6*4*, because all **4* subvariants share 1846G>A causing aberrant splicing and absence of functional protein. For *CYP2D6*2*, however, it is uncertain whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because test laboratories do not discriminate the suballeles. In addition, there are numerous known variants and subvariants of uncertain function that have not been designated by PharmVar at this time (investigators and clinical laboratories are encouraged to submit novel information to PharmVar).

The accuracy of a genotype test depends on the number of sequence variations/allelic variants tested. If no variation is found, a *CYP2D6*1* will be the 'default' assignment. Depending on

which sequence variations are found, the default assignment will be *CYP2D6*2* (or other). For example, if 2851C>T is present, but 1022C>T is not, the default assignment is *CYP2D6*2*. Also see 'CYP2D6 Other Considerations' below.

Note that the SNP positions provided above and below are according to the NG_008376.3 reference sequence. The M33388 "legacy" sequence contains errors causing certain SNP positions to shift by 1-base when mapped to the current reference sequence NG_008376.3. PharmVar uses NG_008376.3 as the 'gold standard' and strongly encourages the use and reporting of positions in respect to the current NG_008376.3 RefSeq. To facilitate SNP mapping, PharmVar cross-references positions between NG_008376.3 and M33388 (https://www.pharmvar.org/gene/CYP2D6).

Recent findings indicate that a SNP in a distal enhancer region impacts allele activity on the transcriptional level (17, 18). It is not fully understood on which allelic variants this enhancer SNP is located. Emerging knowledge, however, suggests that a portion of *CYP2D6*2* alleles carrying the enhancer SNP convey normal function while others lacking the enhancer SNP have decreased function; the effect of the enhancer SNP in other haplotypes remains unknown. Presence or absence of the enhancer SNP potentially impacts the activity encoded by *CYP2D6*2xN* (duplications and multiplications). This SNP is, however, not included in current test panels or allele definitions. The activity score will be updated, if warranted, as new information becomes available.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Clinical laboratories may analyze for different SNPs or other genetic variants, which are dependent on the genotyping platforms used and may affect the reported diplotype leading to discrepant results between methodologies. Additionally, laboratories may differ in how *CYP2D6* copy number variants are reported, which can potentially affect phenotype prediction. Therefore, it is important to not only know the alleles interrogated by each laboratory, but also which sequence variants (e.g., SNPs, insertions, or deletions) are tested and how copy number variants

are reported. Clinical laboratories commonly give an interpretation of the genotype result and provide a predicted phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data but may differ from some clinical laboratory interpretations. Any *CYP2D6* genotyping results used to guide patient pharmacotherapy and/or deposited into patient medical records should be derived from validated genotyping platforms in clinical laboratories that implement the appropriate regulatory standards and best practices (e.g., CAP, CLIA).

CYP2D6 Other Considerations

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Laboratories providing genetic testing usually ignore the contribution of environmental variables such as taking CYP2D6 inhibitors when reporting CYP2D6 phenotypes. **2)** Because it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping tests may not detect rare variants resulting in patients being assigned a default genotype. It also needs to be stressed that genotyping tests are not designed to detect unknown/de novo sequence variations. Depending on the sequence variations (or alleles present) in a given patient, the default genotype may be *CYP2D6*1/*1* (or wild-type) or another diplotype. If the rare or *de novo* variant adversely affects CYP2D6 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** Sub-alleles of *CYP2D6*4* have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2D6*4A*, **4B*, **4C*, and **4D*). Therefore, only analyzing for the defining *CYP2D6*4* SNPs (1847G>A) is usually sufficient to determine a CYP2D6 phenotype. **4)** There are multiple gene units involved in duplication and other major rearrangements. Additionally, the pseudogenes *CYP2D7* and *CYP2D8* may be misinterpreted as functional duplications (19). If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate and CYP2D6 activity over-estimated. **5)** Some SNPs exist on multiple alleles. For example, *CYP2D6*69* carries the defining SNPs for *CYP2D6*41* (2851C>T, 2989G>A, and 4181G>C) and the defining SNPs for *CYP2D6*10* (100C>T and 4181G>C) in addition to multiple other SNPs. If a patient carries these genetic variants (in the absence of 1847G>A), a *CYP2D6*10/*41* diplotype is typically assigned, because this is the most likely result based on allele frequencies. However, a *CYP2D6*1/*69* genotype cannot be excluded with certainty. Testing for additional SNPs (e.g., 1061A>G, 3385A>C, and 3585G>A) could exclude *CYP2D6*1/*69* with certainty. Therefore, to

unequivocally determine the presence of certain alleles, testing for multiple SNPs may be required. **6)** Allele frequencies may vary considerably among individuals of different ethnic backgrounds. For instance, *CYP2D6*10* is common in Asian populations while *CYP2D6*17* is common in people of Sub-Saharan African ancestry. These alleles, however, have a considerably lower prevalence in other ethnic groups such as Caucasians of European ancestry. As another example, *CYP2D6*14* is present in Asian populations and therefore its defining SNP (1759G>A) has been incorporated into Asian genotyping panels (20). Thus, the alleles that should be tested for a given population may vary considerably. **7)** Certain alleles carry genes in tandem arrangements. One such example is *CYP2D6*36+*10* (one copy of the non-functional *CYP2D6*36* and one copy of the decreased function *CYP2D6*10*). This tandem can be found in Asians and is typically reported as a default assignment of *CYP2D6*10*.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Supplemental Table S1** is graded (21) on a scale of high, moderate, and weak, based upon the level of evidence:

> **High:** Evidence includes consistent results from well-designed, well-conducted studies.
>
> **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
>
> **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations (**Table 2**, main manuscript).

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing CYP2D6, in vitro

CYP2D6 enzyme activity from tissues isolated from individuals of known *CYP2D6* genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (22):

Strong recommendation for the statement**:** "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."
Moderate recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (23-27). Resources to support the adoption of CPIC guidelines within an EHR are available on the CPIC website (1, 28). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2D6* genotype results in an EHR to guide atomoxetine use.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (12). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main**

manuscript; *CYP2D6* Diplotype to Phenotype Table (1, 4)). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Atomoxetine Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts; (1, 4, 29, 30).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2D6* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see (1, 27))**.** Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (1).

SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2D6* TO ATOMOXETINE PHENOTYPE

Type of Experimental Model (In vitro, clinical, *ex vivo*)	Major Findings	References	Consensus
In vitro	Allelic variation in *CYP2D6* is association with atomoxetine clearance in vitro (intrinsic clearance).	Liang, *et al*. (2016) (31) Shen, *et al*. (2007) (6)	High
Ex vivo, Clinical	Significant correlation between the number/resulting function of *CYP2D6* variant alleles and metabolism of atomoxetine.	Dinh, *et al*. (2016) (32) Farid, *et al*. (1985) (33) Kim, *et al*. (2016) (34)	High
Ex vivo, Clinical	CYP2D6 PMs have decreased metabolism of atomoxetine as compared to CYP2D6 non-PMs.	Ring, *et al*. (2002) (35) Sauer, *et al*. (2003) (36) *only PM alleles genotyped* Trzepacz*, et al*. (2008) (37) *only PM alleles genotyped* Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Brown, *et al*. (2016) (39)	High
Clinical	Atomoxetine plasma exposure is related to response.	Michelson, *et al*. (2007) (38)	Moderate
Clinical	CYP2D6 PMs have decreased metabolism of atomoxetine as compared to CYP2D6 IMs.	Brown, *et al.* (2016) (39)	Moderate
Clinical	CYP2D6 IMs have decreased metabolism of atomoxetine as compared to CYP2D6 NMs with AS=1.	Brown, *et al*. (2016) (39)	Moderate
Clinical	Subjects with *CYP2D6 *10/*10* genotype have decreased metabolism of atomoxetine as compared to CYP2D6 NMs with AS=2.	Byeon, *et al.* (2015) (40) Matsui, *et al*. (2012) (41) Cui, *et al*. (2007) (42)	High
Clinical	Subjects with *CYP2D6 *10/*10* genotype have decreased metabolism of atomoxetine as compared to *CYP2D6 *10*/normal function allele genotype.	Byeon, *et al*. (2015) (40) Matsui, *et al*. (2012) (41)	High

Clinical	Subjects with *CYP2D6 *10*/normal function allele genotype have decreased metabolism of atomoxetine as compared to CYP2D6 NMs with AS=2.	Byeon, *et al*. (2015) (40) Matsui, *et al*. (2012) (41)	Moderate
Clinical	CYP2D6 PMs have decreased metabolism of atomoxetine as compared to subjects with the *CYP2D6*10/*10* genotype.	Matsui, *et al*. (2012) (41)	Weak
Clinical	CYP2D6 PM are associated with an increased occurrence of treatment-emergent side effects.[a]	Fijal, *et al*. (2015) (43) Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped*	High
Clinical	CYP2D6 PM are associated with an increase in pulse and diastolic blood pressure compared to CYP2D6 non-PM.	Fijal, *et al*. (2015) (43) Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped* Brown, *et al*. (2016) (39)	Moderate
Clinical	No association found between subjects with CYP2D6 AS 0.5-1.5 and CYP2D6 AS 2 and greater with regards to increased occurrence of treatment-emergent side effects[a].	Fijal, *et al*. (2015) (43)	Moderate
Clinical	No association found between subjects with CYP2D6 AS 0.5-1.5 and CYP2D6 AS 2 and greater with regards to increase in pulse and diastolic blood pressure.	Fijal, *et al*. (2015) (43)	Moderate
Clinical	No association found between *CYP2D6*10/*10* and CYP2D6 NM with AS 1.5 or 2 with an increased frequency or severity of side effects[a].	Matsui, *et al*. (2012) (41) Cui, *et al*. (2007) (42)	Weak
Clinical	Subjects with CYP2D6 AS 0.5 or 1 ceased atomoxetine treatment at 1.2 mg/kg dose because of adverse events.	ter Laak, *et al*. (2010) (44)	Moderate
Clinical	CYP2D6 is associated with atomoxetine-associated weight changes.	Fijal, *et al*. (2015) (43) Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped* Fijal, *et al*. (2015) (43)	Weak

Clinical	Percentage of responders[b] is increased in CYP2D6 PMs compared to CYP2D6 non-PMs.	Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped*	Moderate
Clinical	CYP2D6 PMs are associated with greater improvement of ADHD symptoms compared to CYP2D6 non-PMs.	Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped* Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Ramoz, *et al*. (2009) (45) *PM grouping unclear either PM/PM or PM/PM + NM/PM* Asherson, *et al*. (2014) (46)	Moderate
Clinical	CYP2D6 non-PMs are associated with increased discontinuation due to lack of efficacy compared to CYP2D6 PMs.	Michelson, *et al*. (2007) (38) *only PM alleles genotyped* Trzepacz, *et al*. (2008)(37) *only PM alleles genotyped*	Moderate
Clinical	No difference found between CYP2D6 PMs and non-PMs in regards to discontinuation due to side effects.	Trzepacz, *et al*. (2008) (37) *only PM alleles genotyped* Michelson, *et al*. (2007) (38) *only PM alleles genotyped*	Moderate
Clinical	CYP2D6 PMs are associated with lower doses compared to CYP2D6 non-PMs.	Todor, *et al*. (2015) (47) *only PM alleles genotyped* Michelson, *et al*. (2007) (38) *only PM alleles genotyped*	High
Clinical	Atomoxetine metabolism is decreased during co-administration of CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion) in non-PM metabolizers.	Kratochvil, *et al*. (2005) (48) Todor, *et al*. (2015) (47) Kim, *et al*. (2016) (34) Todor, *et al*. (2016) (49) Belle, *et al*. (2002) (50) Paulzen, *et al*. (2008) (51)	High
Clinical	Cardiovascular side effects after atomoxetine and fluoxetine co-medication.	Paulzen, *et al*. (2008) (51) Naguy, *et al*. (2016) (52)	Weak

Clinical	Increased heart rate and diastolic blood pressure with atomoxetine and fluoxetine co-medication compared to atomoxetine alone.	Kratochvil, *et al*. (2005) (48)	Moderate
Clinical	Decrease in weight with atomoxetine and fluoxetine co-medication compared to atomoxetine alone.	Kratochvil, *et al*. (2005) (48)	Moderate
Clinical	Greater reduction in CDI scores but not other outcome measurements with atomoxetine and fluoxetine co-medication compared to atomoxetine alone.	Kratochvil, *et al*. (2005) (48)	Moderate
Clinical	Co-administration of paroxetine increased atomoxetine levels and resulted in improved response in one adult.	Paulzen, *et al*. (2008) (51)	Weak

[a]See references and discussion in guideline/supplement for list of side effects.
[b]Based on ADHD Rating Scale-IV-Parent Version: Investigator -administered and -scored (ADHDRS-IV-Parent:Inv) scale
Abb.: CDI = Children's Depression Inventory; AS = activity score; PM = poor metabolizer; NM = normal metabolizer; IM = intermediate metabolizer

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