**Discovering Interactions in Augmentation Strategies:   
Impact of Duloxetine on the Metabolism of Aripiprazole**

**Running Title: Inhibition of aripiprazole metabolism by duloxetine**

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**a) Running title page**

Enhancement of aripiprazole by duloxetine

**b)** **The number of text pages, number of tables, figures, and references, and the number of words in the Abstract, Introduction, and Discussion**

number of text pages: 10 (double-spaced)

number of tables: 2

number of figures: 3

number of references: 39

number of words in the abstract: 194

number of words in the introduction: 612 (including references);

number of words in the materials and methods section: 748 (including references);

number of words in the results section: 274 (including references);

number of words in the discussion: 802 (including references and limitations);

number of words in the manuscript: 2,436 (including headings and references)

**Abstract**

**Objective:**

Combining different drugs increases the potential for drug-drug interactions enhancing the risk of adverse drug reactions. We aimed to unravel potential pharmacokinetic interactions between aripiprazole and duloxetine.

**Methods:**

Plasma concentrations of aripiprazole of two groups of 78 patients each, receiving aripiprazole as a monotherapy, or combined with duloxetine, were compared. A potential impact of duloxetine on the metabolism of aripiprazole was expected in higher plasma concentrations of aripiprazole and higher dose-adjusted plasma concentrations.

**Results:**

Patients co-medicated with duloxetine showed significantly higher plasma concentrations of aripiprazole (p=0.019) by 54.2%. Dose-adjusted plasma concentrations were 45.6% higher (p=0.001). 65.4 % of these patients exhibited aripiprazole plasma concentrations above the upper limit of the therapeutic reference range, in the control group this was only the case for 43.6% of the patients (p=0.006). A positive relationship was found between the daily dose of duloxetine and dose-adjusted plasma concentrations of aripiprazole (p=0.034).

**Conclusions:**

Combining duloxetine and aripiprazole leads to significantly higher drug concentrations of aripiprazole, most likely via an inhibition of cytochrome P450 CYP2D6 and to a lesser extent of CYP3A4 by duloxetine. Clinicians have to consider increasing aripiprazole concentrations when adding duloxetine to a treatment regimen with aripiprazole.

**Funding:** None.

**Data Sharing**: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Key Words:** Therapeutic Drug Monitoring – Aripiprazole – Duloxetine – Pharmacokinetics – Cytochrome – Interaction

**Statements of Interest:** Dr. Haen received speaker’s or consultancy fees from the following pharmaceutical companies: Servier, Novartis, and Janssen-Cilag. He is managing director of AGATE. He is editor of an internet-based drug-drug interaction program (www.psiac.de). He reports no conﬂict of interest with this publication. Dr. Paulzen has received speaker’s fees from Janssen, ROVI, Neuraxpharm, Lundbeck and Otsuka. He has served as a consultant for Novartis, Otsuka and ROVI. He is editor of an internet-based drug-drug interaction program (www.psiac.de). He reports no conﬂict of interest with this publication. Dr. Schoretsanitis has served as a consultant for HLS Therapeutics and Thermo Fisher and has received speaker's fees from HLS Therapeutics. All other authors report no conflicts of interests.

**Authorship contributions**

Participated in research design: TM, MP, AG, GS, EH.

Performed analytic tools: EH

Performed data analysis: TM, AG.

Wrote the manuscript: TM

Edited and corrected the manuscript: MP, AG, GS, IN

**What is known:**

* Pharmacokinetic interactions are of high clinical relevance even in complex clinical situations.
* Little is known about pharmacokinetic interactions between aripiprazole and duloxetine.
* Previous evidence suggests moderate inhibitory effects for duloxetine on cytochrome P450 enzymes (CYP) 2D6.

**What this study adds**:

* Co-medication with duloxetine is associated with significantly higher (54.2 %) plasma concentrations of aripiprazole (ARI) compared to ARI monotherapy.
* Dose adjusted plasma concentrations (C/D ratio) of ARI were 45.6 % higher in the duloxetine co-medication group.
* Findings suggest a relevant pharmacokinetic interaction, most likely via a CYP 2D6 inhibition.

**Limitations**

Our sample comprised a large naturalistic population and relies on retrospective data. The database consists only of aripiprazole but not of dehydroaripiprazole concentrations. Therefore, conclusions for the active moiety, the sum of aripiprazole plus dehydroaripiprazole, and the metabolic ratio cannot be drawn.

**Introduction**

Augmentation strategies, i.e. combining psychopharmacological agents of different drug classes such as antipsychotics and antidepressants, are clinically widespread1. By using adjunctive antidepressants, clinicians intend to improve the treatment outcomes, specifically targeting negative or cognitive symptoms in schizophrenia2,3, whereas such treatment strategies are of proven benefit for antidepressant-refractory depression4.

Combining an atypical antipsychotic such as aripiprazole and a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) such as duloxetine, is found to be advantageous also in early onset schizophrenia5. Both, randomized, double-blind and placebo-controlled trials and meta-analyses showed small but significant effects of duloxetine on reducing negative symptoms and improving general psychopathology in patients with schizophrenia6,7. Clayton et al. studied the effect of combined treatment of major depressive disorder with aripiprazole and both, SSRI or SNRI. The combination led to symptom improvement over 52-weeks8. Mohamed et al. also studied the combined treatment of aripiprazole with an SSRI or SNRI for treatment resistant major depressive disorder and confirmed increased remission rates9. Duloxetine is an antidepressant of the SSNRI group. It is a strong reuptake inhibitor of serotonin and norepinephrine and an effective drug for the treatment of major depressive disorder, generalized anxiety disorder, diabetic neuropathic pain, stress urinary incontinence and fibromyalgia10. The therapeutic reference range for duloxetine is suggested at 30-120ng/mL11. Duloxetine is metabolized by CYP1A2 and CYP2D6, while knowledge about the role of duloxetine as a so-called perpetrator drug, impacting the metabolism of concomitantly applied drugs, that are substrates of CYP 2D6, is limited12,13. Early data suggest inhibitory effects of duloxetine on cytochrome P450 2D6 mediated metabolism of desipramine, enhancing the maximum plasma concentration of desipramine 1.7-fold and the area under the concentration-time curve, AUC, 2.9-fold12,14, while effects of duloxetine on the metabolism of other psychotropic medications, including CYP2D6 substrates, remain poorly understood.

Aripiprazole is an atypical antipsychotic approved by the US Food and Drug Administration for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with Bipolar I disorder, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder and treatment of Tourette’s disorder15.

Aripiprazole acts primarily as a partial agonist at the dopamine-D2-, dopamine-D3- and serotonin 5-HT1A-receptor and exerts antagonist activities at serotonin 5-HT2A-receptors16-18. Aripiprazole is nearly equally metabolized in the liver by the two cytochromes P450 enzymes CYP2D619 and CYP3A420 via dehydrogenation, hydroxylation and N-dealkylation into its primary active metabolite dehydroaripiprazole21. The update of the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology, as well as the Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, suggest a therapeutic reference range (TRR) for aripiprazole as 100-350ng/mL and for the so-called active moiety, the sum of aripiprazole plus dehydroaripiprazole as 150-500 ng/mL, respectively11,22.

Therapeutic drug monitoring (TDM) is a specific method of clinical pharmacology that can be successfully used to guide psychopharmacological treatment in clinical routine by determining plasma concentrations of applied drugs. Pharmacokinetic drug-drug interactions can be uncovered using TDM by identifying different pharmacokinetic patterns such as changes in plasma concentrations of the parent compound, its metabolites, changes in metabolite-to-parent-ratios, MPR, (quotient of drug concentration of the metabolite and the parent compound) or differences in dose adjusted drug concentrations, the so-called concentration to dose value (C/D). TDM databases with huge numbers of plasma concentration samples allow the evaluation of pharmacokinetic drug-drug-interactions (DDIs) in naturalistic study samples and can provide insights into potential interactions, safety and tolerances of combined psychopharmacological treatments11,23,24.

Based on a TDM database we aimed to shed light on a potential pharmacokinetic DDI between aripiprazole and duloxetine by comparing a group of patients treated with aripiprazole as a monotherapy and patients receiving a combined treatment of aripiprazole and duloxetine.

**Methods**

A large database as part of KONBEST, a web-based laboratory information management system for therapeutic drug monitoring-laboratories, consisting of more than three thousand plasma concentrations of aripiprazole, was used25. Data collection took place between 2006 and 2019 as a part of the clinical routine in different institutions of AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychischen Erkrankungen). AGATE is a cooperation for drug safety and efficacy in the treatment of psychiatric diseases (for details: www.amuep-agate.de).

In the case of multiple plasma concentrations of aripiprazole for one patient available, only the most recent concentration was used for our analysis. Patients receiving long-acting-injectable formulations (LAI) were excluded from the analysis. According to suggestions by the US Food and Drug Administration, we also excluded patients receiving concomitant medications with possible inhibitory or inducing properties for CYP3A4 and possible inhibitory properties for CYP2D611. Using these criteria, we obtained a sample of 1,942 patients with different psychiatric conditions under medication with either aripiprazole monotherapy or co-medicated with duloxetine. Within this sample we considered two groups: a group that was co-medicated with duloxetine (ARIDLX, n=78, median of duloxetine dose = 90 mg [Q1=60 mg, Q3=120 mg]) and a control group receiving aripiprazole without duloxetine (ARI, n=78). Out of 1,492 patients receiving aripiprazole, we matched 78 patients as control group with respect to sex, age, weight, nicotine and caffeine consumption as well as the daily dosage of aripiprazole. Additional matching processes, i.e. for diagnoses, severity of illness, length or onset of illness were not undertaken. As all participating institutions are experienced in therapeutic drug monitoring and participants are requested to draw blood at trough level times under steady-state conditions, it can be assumed that data reflect optimal TDM circumstances. All procedures involving human subjects/patients were approved by the RWTH-Aachen University regulatory authority.

**Chromatographic determination of aripiprazole**

For the quantification of aripiprazole, blood samples were asked to be taken right before drug administration (trough levels) at steady-state conditions (>5 elimination half-lives under the same drug dose). Aripiprazole plasma concentrations were detected in the same laboratory by high performance liquid chromatography with ultraviolet detection (HPLC/UV)26. Unfortunately, plasma concentrations of dehydroaripiprazole were not available. The quantification process was authorized according to DIN 32645 (Deutsche Industrie Norm 32,645 mentioned in the guidelines of the GTFCh (Society of Toxicology and Forensic Chemistry) in view of ICH (International Conference on Harmonization)27, FDA (US Food and Drug Administration, 2018)28 and in consideration of ISO 5725 (International Organization for Standardization)29. Quality controls are performed routinely from the laboratory and it further cooperates with INSTAND (Düsseldorf, Germany, www.instandev.de) for external quality assessment schemes.

Inaccuracy, inter- and intraday imprecision values were calculated for aripiprazole concentrations of 600, 300 and 50 ng/mL.

* Inaccuracy: bias values were 0,95%, 3,79% and -0,13%.
* Interday imprecision: coefficients of variation (CV) were 7,4%, 5,9% and 6,7%.
* Intraday imprecision. CVs were 0,3%, 0,6% and 4,1%

The limit of detection (LOD) was 5,1 ng/mL and the limit of quantification (LOQ) was 10,2 ng/mL, respectively.

**Statistical analysis**

The statistical analysis included the comparison of drug concentrations of the two study groups. Dose-adjusted drug concentrations (ratio of the drug concentration C and the applied daily dose D, C/D, in [(ng/mL)/(mg/day)]) for ARIDLX and ARI were also calculated. Histograms showed evidence of non-normal distributions, so a non-parametric Mann Whitney-*U*-test (MWU) with a significance level of 0.05 was performed to compare the distributions of plasma concentrations and dose-adjusted drug concentrations between ARIDLX and ARI. Mann Whitney-*U*-test with the same significance level was applied to compare weight and BMI, due to non-normal distributions. χ2 – tests were conducted to compare the sex-, nicotine- and caffeine consumption ratio between   
ARIDLX and ARI with a significance level of 0.05. To further elucidate the effect of the co-administration of duloxetine on the aripiprazole concentrations with regard to the recommended therapeutic reference range, we compared the percentage of patients with plasma concentrations above or below the upper limit of the therapeutic reference range (TRR) = 350 ng/mL as proposed by the AGNP consensus guidelines11 between the two groups using a χ2-test. Finally, we explored the relationship between the daily dose of duloxetine and the dose-adjusted concentrations of aripiprazole (C/D), using regression and correlation analysis. Inspection of the residuals and Q-Q-plots of the linear regression analysis motivated us to use Spearman’s rank correlation coefficient as a more conservative measure to test this relationship.

Statistical analysis was carried out using MATLAB (The MathWorks, Inc., Natick, USA), SPSS (IBM, Armonk, USA) and RStudio (RStudio Team (2021). RStudio: Integrated Development Environment for R30. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

**Results**

Sociodemographic data of the two study groups are summarized in table 1. The control group (ARI) and the duloxetine group (ARIDLX) did not differ in terms of age (*p*=0.845), weight (*p*=0.704), BMI (*p*=0.965), sex (*p*=0.999), nicotine consumption (*p*=0.626), caffeine consumption (*p*=0.357) or daily dosage of aripiprazole (*p*=0.973). Median daily doses of aripiprazole were 10mg (Q1=7.5 mg; Q3=15 mg) for both groups (p=0.973).

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| **Table 1.** Sociodemographic and clinical characteristics of the study sample consisting of patients receiving aripiprazole as a monotherapy or in a combined regimen with duloxetine. | | | | | | | | | |
| Characteristic | Aripiprazole + Duloxetine (n=78) | | | Aripiprazole (n=78) | | | Comparison | |
|  | median | Q1 | Q3 | median | Q1 | Q3 | Wa | p |
| age [years] | 48.5 | 40 | 63 | 49 | 40 | 62 | 6178.5 | 0.845 |
| dose of aripiprazole [mg/day] | 10 | 7.5 | 15 | 10 | 7.5 | 15 | 6113.5 | 0.973 |
| weight [kg] | 88.5 | 77 | 100 | 89 | 82 | 99 | 6015.5 | 0.704 |
| BMI [kg/m2] | 29 | 27 | 35 | 29 | 27 | 35 | 6135.5 | 0.965 |
|  | n |  | % | n |  | % | χ2 (df = 1) | p |
| sex | 78 |  |  | 78 |  |  | 0 | 1 |
| female | 43 |  | 55 | 43 |  | 55 |  |  |
| male | 35 |  | 44 | 35 |  | 44 |  |  |
| nicotine consumption |  |  |  |  |  |  | 0.237 | 0.626 |
| smokers | 44 |  | 56.4 | 47 |  | 60.2 |  |  |
| non-smokers | 34 |  | 43.5 | 31 |  | 39.7 |  |  |
| caffeine consumption |  |  |  |  |  |  | 0.846 | 0.357 |
| consumers | 65 |  | 83 | 69 |  | 88.4 |  |  |
| non-consumers | 13 |  | 16 | 9 |  | 11.5 |  |  |
| a Due to non-normality of some variables, Mann Whitney-U-test was consistently chosen to assess group differences. W represents the smaller rank-sum of the two groups, respectively. | | | | | | | | | |

Median aripiprazole plasma concentrations (ng/mL) in the ARI- and ARIDLX-group, as well as the dose-adjusted plasma concentrations, are displayed in table 2.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2.** Aripiprazole plasma concentrations and dose adjusted plasma concentrations (C/D) obtained from patients receiving aripiprazole as a monotherapy or in a combined regimen with duloxetine. | | | | | | | | | |
| Characteristic | Aripiprazole + Duloxetine (n=78) | | | Aripiprazole (n=78) | | | Comparison | |
|  | Median | Q1 | Q3 | Median | Q1 | Q3 | Wa | p |
| Aripiprazole concentration [ng/mL] | 200.5 | 120.0 | 289.0 | 130.0 | 81.0 | 255.0 | 6784 | 0.02 |
| C/D value [(ng/mL)/(mg/day)] | 17.40 | 14.17 | 19.13 | 11.95 | 8.80 | 19.80 | 7064 | 0.001 |
| aDue to non-normality of these variables, Mann Whitney-*U*-test was consistently chosen to assess group differences. W represents the smaller rank-sum of the two groups, respectively. | | | | | | | | | |

Patients that were co-medicated with duloxetine showed significantly higher plasma concentrations of aripiprazole (median 200.5 vs. 130.0 ng/mL, *p*= 0.019). On a descriptive level, the median plasma concentration was 54.2% higher in the ARIDLX group (see figure 1).

“Place fig. 1 here”

**Figure 1** By combining duloxetine with aripiprazole, the median plasma concentration of aripiprazole was 54.2% higher (left) than in the control group (right), p=0.019.

We also detected higher dose-adjusted plasma concentrations of aripiprazole (C/D) in the ARIDLX group by 45.6% compared to the ARI group (*p*=0.001, figure 2).

Place “fig. 2” here

**Figure 2** By combining duloxetine with aripiprazole, the dose-adjusted plasma concentration of aripiprazole was 45.6% higher (left) than in the control group (right), p=0.001.

To explore the proportion of patients, whose drug concentrations exceeded the therapeutic reference range (TRR), we identified 51 patients (65.4%) above and 27 (34.6%) below the upper limit of the TRR in the ARIDLX group. In contrast, in the ARI group only 34 patients (43.6%) had drug concentrations above and 44 patients (56.4%) showed drug concentrations below the upper limit of the TRR. The respective group difference was statistically significant (χ2(df =1) = 7.47; p = 0.006).

Finally, we also aimed to find out, whether duloxetine exerted its effect on aripiprazole concentrations in a dose dependent manner. A respective scatter plot indeed suggested a positive relationship between the applied daily duloxetine dose and dose-adjusted plasma concentrations of aripiprazole (see figure 3) which was statistically significant (rho=0.24; p=0.034).

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**Figure 3** Relationship between the daily duloxetine dose and dose-adjusted plasma concentrations (C/D) of aripiprazole.

**Discussion**

Numerous clinical situations such as treatment-resistant depression, poor treatment outcome with persisting negative symptoms in schizophrenia, bipolar disorder or depressive episodes all along with schizophrenia, require augmentation strategies, such as a combination of antipsychotic drugs with antidepressants9,31-33. Little is known about pharmacokinetic drug-drug interactions between aripiprazole and duloxetine that claim a common metabolic pathway via cytochrome P450 isoenzyme CYP2D6. We sought to shed light on CYP2D6 mediated interaction by analyzing a database of a naturalistic sample of psychiatric patients in different institutions of AGATE treated for various clinical reasons with either aripiprazole alone or with a combined treatment of aripiprazole and duloxetine.

Co-medicated patients showed aripiprazole plasma concentrations that were more than fifty percent (54.2%) higher than in patients not receiving duloxetine. Concomitantly applied duloxetine led to dose-adjusted plasma concentrations of aripiprazole that were 46.4 % higher than in patients receiving a monotherapy with aripiprazole. Moreover, the co-medication was associated with a significantly higher percentage of patients exhibiting aripiprazole concentrations above the therapeutic reference range. Both groups were matched for demographics as well as for daily dosage. Thus, differences in pharmacokinetic patterns cannot be explained by differences in aripiprazole’s daily dosages. Higher plasma concentrations in the ARIDLX-group are rather the consequence of the fact that aripiprazole and duloxetine share the same metabolic pathway with duloxetine exerting inhibitory properties on cytochrome CYP2D6. Inhibitory effects of duloxetine on CYP2D6 decrease the metabolism of aripiprazole as evidenced by higher plasma concentrations of aripiprazole and higher dose-adjusted plasma concentrations.

To our knowledge there is only one case report describing a potential inhibitory effect of duloxetine on CYP2D6 mediated metabolism of aripiprazole, thereby increasing aripiprazole drug concentrations. This single case showed increased aripiprazole serum concentrations in a 43-year old male patient receiving a medication with aripiprazole, duloxetine, ritonavir and darunavir, the latter inhibiting both, CYP3A4 and CYP2D634. Hence, in this case it remains unclear, if the combination of these drugs or just one single drug was responsible for the increased concentration of aripiprazole. Our study group was free of any other potential perpetrators such as CYP2D6 or CYP3A4 inhibitors or inducers and showed more than fifty percent higher concentrations than the control group. This could indicate that duloxetine has a stronger effect on the metabolism of aripiprazole than previously reported in clinical routine, although early *in vitro* data in human liver microsomes already suggested a relatively high potency of duloxetine to inhibit CYP2D6, 2B6 and even CYP3A4/535.

Previous studies emphasized an important influence of genetic polymorphism of the polymorphic CYP2D6 on the pharmacokinetics of aripiprazole. This could explain differences in plasma concentrations between two groups as well36. More than 20 alleles of *CYP2D6* were identified in healthy Japanese, showing that the *CYP2D6* genotype impacts the metabolism of CYP2D6 metabolized drugs37. Belmonte and Hendset showed, that poor metabolizers (PM) with a lack of function of CY2D6 had higher concentrations of aripiprazole than extensive metabolizers (EM) and aripiprazole dose adjustments were needed to reach equivalent plasma concentrations19,38. As *CYP2D6* genotypes were not available in our database, we cannot comment on this potentially influencing factor. However, a group size of 78 in both groups may reduce the impact of genetic variances. This leads to the conclusion that the higher concentrations of aripiprazole are a consequence of inhibiting properties of duloxetine on either CYP2D6, CYP3A4 or both.

To our knowledge, there is only one other study investigating the influence of duloxetine on the metabolism of aripiprazole as a co-medication. Hendset et al. analyzed changes in plasma concentrations and metabolic ratios (dehydroaripiprazole/aripiprazole) in seven patients under a combined treatment with aripiprazole and duloxetine. The co-administration of duloxetine neither increased the concentration of aripiprazole nor changed the parent drug/metabolite ratio of aripiprazole39. Our larger sample size offers new insights in potentially occurring DDIs between duloxetine and aripiprazole. To better elucidate the clinical relevance of the DDI reported in our sample, more clinically relevant information as well as information about the drug concentration of dehydroaripiprazole is mandatory. Even though our study shows a significant impact of duloxetine on the concentration of aripiprazole, further studies are necessary to confirm and understand why there are divergent findings.

Summing up, our results support the use of therapeutic drug monitoring in combination treatment strategies when treating patients with psychiatric disorders in clinical settings11. The combination of aripiprazole and duloxetine may affect the metabolism of aripiprazole leading to higher aripiprazole concentrations due to a reduced clearance. Dose titration should be individualized when patients receive a combined treatment with aripiprazole and duloxetine. TDM can be precisely used to increase the safety and tolerability of antipsychotic treatment.

**Limitations**

Our sample comprised a large naturalistic population and relies on retrospective data. The database consists only of aripiprazole but not of dehydroaripiprazole concentrations. Therefore, conclusions for the active moiety, the sum of aripiprazole plus dehydroaripiprazole, and the metabolic ratio cannot be drawn.

**References**

1. Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA Psychiatry*. May 1 2019;76(5):499-507. doi:10.1001/jamapsychiatry.2018.4320

2. Galling B, Vernon JA, Pagsberg AK, et al. Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia. *Acta Psychiatr Scand*. Mar 2018;137(3):187-205. doi:10.1111/acps.12854

3. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 Pharmacologic Cotreatment Strategies Added to Antipsychotic Monotherapy in Schizophrenia: Systematic Overview and Quality Appraisal of the Meta-analytic Evidence. *JAMA Psychiatry*. Jul 1 2017;74(7):675-684. doi:10.1001/jamapsychiatry.2017.0624

4. Furukawa Y, Hamza T, Cipriani A, Furukawa TA, Salanti G, Ostinelli EG. Optimal dose of aripiprazole for augmentation therapy of antidepressant-refractory depression: preliminary findings based on a systematic review and dose-effect meta-analysis. *Br J Psychiatry*. Aug 2022;221(2):440-447. doi:10.1192/bjp.2021.165

5. Pridmore S, Naguy A, Moodliar-Rensburg S, Alamiri B. Advantageous Add-on Duloxetine to Aripiprazole-Responsive Early-Onset Schizophrenia. *J Clin Psychopharmacol*. Jan/Feb 01 2021;41(1):91-92. doi:10.1097/JCP.0000000000001313

6. Mico U, Bruno A, Pandolfo G, et al. Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: a randomized, placebo-controlled trial. *Int Clin Psychopharmacol*. Nov 2011;26(6):303-10. doi:10.1097/YIC.0b013e32834bbc0d

7. Nikbakhat MR, Arabzadeh S, Zeinoddini A, et al. Duloxetine Add-On to Risperidone for Treatment of Negative Symptoms in Patients with Stable Schizophrenia: Randomized Double-Blind Placebo-Controlled Study. *Pharmacopsychiatry*. Jul 2016;49(4):162-9. doi:10.1055/s-0042-101557

8. Clayton AH, Baker RA, Sheehan JJ, et al. Comparison of adjunctive use of aripiprazole with bupropion or selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors: analysis of patients beginning adjunctive treatment in a 52-week, open-label study. *BMC Res Notes*. Jul 18 2014;7:459. doi:10.1186/1756-0500-7-459

9. Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *JAMA*. Jul 11 2017;318(2):132-145. doi:10.1001/jama.2017.8036

10. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. May 2011;50(5):281-94. doi:10.2165/11539240-000000000-00000

11. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry*. Jan 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

12. Skinner MH, Kuan HY, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. *Clin Pharmacol Ther*. Mar 2003;73(3):170-7. doi:10.1067/mcp.2003.28

13. Shelton RC. Serotonin and Norepinephrine Reuptake Inhibitors. *Handb Exp Pharmacol*. 2019;250:145-180. doi:10.1007/164\_2018\_164

14. Patroneva A, Connolly SM, Fatato P, et al. An assessment of drug-drug interactions: the effect of desvenlafaxine and duloxetine on the pharmacokinetics of the CYP2D6 probe desipramine in healthy subjects. *Drug Metab Dispos*. Dec 2008;36(12):2484-91. doi:10.1124/dmd.108.021527

15. US Food and Drug Administration, FDA. Prescribtion information ABILIFY. U.S. Food and Drug Administration. Accessed March 2nd, 2021, <https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021436s041,021713s032,021729s024,021866s026lbl.pdf>

16. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*. Jul 2002;302(1):381-9. doi:10.1124/jpet.102.033175

17. Jordan S, Koprivica V, Chen R, Tottori K, Kikuchi T, Altar CA. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *Eur J Pharmacol*. Apr 26 2002;441(3):137-40. doi:10.1016/s0014-2999(02)01532-7

18. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology*. Aug 2003;28(8):1400-11. doi:10.1038/sj.npp.1300203

19. Hendset M, Hermann M, Lunde H, Refsum H, Molden E. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. *Eur J Clin Pharmacol*. Dec 2007;63(12):1147-51. doi:10.1007/s00228-007-0373-6

20. Waade RB, Christensen H, Rudberg I, Refsum H, Hermann M. Influence of comedication on serum concentrations of aripiprazole and dehydroaripiprazole. *Ther Drug Monit*. Apr 2009;31(2):233-8. doi:10.1097/FTD.0b013e3181956726

21. Castberg I, Spigset O. Effects of comedication on the serum levels of aripiprazole: evidence from a routine therapeutic drug monitoring service. *Pharmacopsychiatry*. May 2007;40(3):107-10. doi:10.1055/s-2007-977715

22. Schoretsanitis G, Kane JM, Correll CU, et al. Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie. *J Clin Psychiatry*. May 19 2020;81(3)doi:10.4088/JCP.19cs13169

23. Schoretsanitis G, Haen E, Gründer G, et al. Pharmacokinetic Drug-Drug Interactions of Mood Stabilizers and Risperidone in Patients Under Combined Treatment. *J Clin Psychopharmacol*. Dec 2016;36(6):554-561. doi:10.1097/JCP.0000000000000601

24. Paulzen M, Haen E, Gründer G, et al. Pharmacokinetic considerations in the treatment of hypertension in risperidone-medicated patients - thinking of clinically relevant CYP2D6 interactions. *Journal of psychopharmacology*. Aug 2016;30(8):803-9. doi:10.1177/0269881116650390

25. Haen E. Therapeutic drug monitoring in pharmacovigilance and pharmacotherapy safety. *Pharmacopsychiatry*. Sep 2011;44(6):254-8. doi:10.1055/s-0031-1286285

26. Ben-Omar N, Haen E. Quantification of eighteen psychotherapeutic agents and their metabolites using column switching HPLC/UV. *Pharmacopsychiatry*. 2015;

27. International Conference on Harmonisation. Harmonised Tripartite Guideline, Validation of Analytical Proce- dures: Test and Methodology. *In: International conference on harmonisation of technical requirements for registration of pharma- ceuticals for human use*. 1996;

28. US Food and Drug Administration, FDA. Guidance for Industry on Biomedical Method Validation. 2018;

29. Paul L MF, Aebi B, et al. . Richtlinie der GTFCh zur Qualitätssicherung bei forensisch-toxikologischen Untersuchungen. *Toxichem Krimtech*. 2009;

30. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [*http://wwwR-projectorg/*](http://wwwR-projectorg/). 2013;

31. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. Mar 2018;20(2):97-170. doi:10.1111/bdi.12609

32. Ruberto VL, Jha MK, Murrough JW. Pharmacological Treatments for Patients with Treatment-Resistant Depression. *Pharmaceuticals (Basel)*. Jun 4 2020;13(6)doi:10.3390/ph13060116

33. Mossaheb N, Kaufmann RM. Role of aripiprazole in treatment-resistant schizophrenia. *Neuropsychiatr Dis Treat*. 2012;8:235-44. doi:10.2147/NDT.S13830

34. Aung GL, O'Brien JG, Tien PG, Kawamoto LS. Increased aripiprazole concentrations in an HIV-positive male concurrently taking duloxetine, darunavir, and ritonavir. *Ann Pharmacother*. Nov 2010;44(11):1850-4. doi:10.1345/aph.1P139

35. Paris BL, Ogilvie BW, Scheinkoenig JA, Ndikum-Moffor F, Gibson R, Parkinson A. In vitro inhibition and induction of human liver cytochrome p450 enzymes by milnacipran. *Drug Metab Dispos*. Oct 2009;37(10):2045-54. doi:10.1124/dmd.109.028274

36. Kubo M, Koue T, Maune H, Fukuda T, Azuma J. Pharmacokinetics of aripiprazole, a new antipsychotic, following oral dosing in healthy adult Japanese volunteers: influence of CYP2D6 polymorphism. *Drug Metab Pharmacokinet*. Oct 2007;22(5):358-66. doi:10.2133/dmpk.22.358

37. Azuma J, Hasunuma T, Kubo M, et al. The relationship between clinical pharmacokinetics of aripiprazole and CYP2D6 genetic polymorphism: effects of CYP enzyme inhibition by coadministration of paroxetine or fluvoxamine. *Eur J Clin Pharmacol*. Jan 2012;68(1):29-37. doi:10.1007/s00228-011-1094-4

38. Belmonte C, Ochoa D, Roman M, et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 Polymorphisms on Pharmacokinetics and Safety of Aripiprazole in Healthy Volunteers. *Basic Clin Pharmacol Toxicol*. Jun 2018;122(6):596-605. doi:10.1111/bcpt.12960

39. Hendset M, Molden E, Enoksen TB, Refsum H, Hermann M. The effect of coadministration of duloxetine on steady-state serum concentration of risperidone and aripiprazole: a study based on therapeutic drug monitoring data. *Ther Drug Monit*. Dec 2010;32(6):787-90. doi:10.1097/FTD.0b013e3181fc50d5