SUPPLEMENTARY MATERIAL FOR
A SYSTEMATIC REVIEW AND COMBINED ANALYSIS OF THERAPEUTIC DRUG

MONITORING STUDIES FOR ORAL PALIPERIDONE

Supplementary Methods section with additional information including 3 subsections

Supplementary Box S1 and Supplementary Box S2

1. SUPPLEMENTARY METHODOLOGICAL ASPECTS

1.1. Supplementary Information on the Article Search

Figure 1 describes the search which identified 514 records from four sources: 1) 13 articles obtained on September 22, 2017, in a PubMed search using the terms ("Paliperidone/blood"[Mesh]); 2) 468 articles from a search in Embase on the same day with the terms ("paliperidone AND 'humans' AND 'drug concentration'"); 3) 29 articles from the files of the first, second and last authors; and 4) 5 articles from the reference lists of other articles. After reviewing all of these 515 abstracts, 44 were considered potentially interesting. Then after careful consideration and discussion by two of the authors, 14 articles were excluded and 30 were selected for review of the full article. Of these 30 articles, 7 were excluded and 23 were considered for systematic review. Included articles are 21 studies [25-37, 42, 43, 74, 76-80] and 2 case reports [43, 81], which are listed in Table 1.

1.2. Pharmacokinetic Quality of the Studies

In the calculation of the mean concentration/dose (C/D) ratio (Table 2), we included 9 studies that provided steady-state data [33, 36, 37, 41, 42, 76, 78-80]. All 9 studies were reviewed by the first and second authors to obtain and/or calculate these ratios. Contamination by confounders cannot be definitely excluded since in some studies the ratios were contaminated through the intake of cytochrome P450 (CYP) or p-glycoprotein (P-gp) inducers or inhibitors and/or renal impairment. Nevertheless, the extent of contamination appears relatively small to the authors, since the prevalence of taking inducers or inhibitors or suffering from renal impairment was probably small.

When estimating drug clearance, rather than completing TDM studies of patients taking repeated doses, the pharmaceutical companies used single-dose studies, frequently in healthy individuals. Drug clearance is computed by calculating the area under the curve (AUC), usually 24 hours after the single dose. These AUC values probably have a linear relationship with C/D ratios under repeated dosing calculated from therapeutic drug monitoring (TDM) studies [82]. Fourteen paliperidone TDM studies (all

marketer studies) provided AUC data which could not be used to calculate paliperidone C/D ratios and were excluded from Table 2 [25-37, 74].

Drug-drug interactions (DDIs) between oral paliperidone and other medications have been sparsely studied. Due to the lack of pharmacokinetic evidence for DDI, when reviewing data, we decided not to exclude case reports of DDIs providing serum or plasma paliperidone concentrations [64, 65]. Apart from the two case reports [43, 81], 5 studies with DDIs provided pharmacokinetic data [35-37, 42]. All 7 studies were reviewed by the first and second authors to obtain and/or calculate alteration ratios for C/D or AUC values (or both when available) before and after receiving the co-medication (on and off). These ratios may reflect the size of the effects resulting from the DDI. Data was available for five pharmacological agents: paroxetine, trimethoprim, carbamazepine, an oral anticancer drug containing 5-fluorouracil derivate, and valproate.

The effects on paliperidone clearance, measured by changes in AUC from personal variables [83] such as aging [29], renal impairment [30] and hepatic impairment [34], are described in Table 4.

1.3. Quality of the Analytical Laboratories

Six studies did not provide any information on the analytical method [26, 29, 30, 32, 43, 81]. Regarding method validation, no further details were provided in eight studies [26, 29, 30-32, 43, 76, 81], while seven studies referred to previously published analytical articles [33-35, 41, 74, 78, 80].

Supplementary Box S1. Pharmacodynamics of paliperidone and risperidone at the cardiac potassium channels

Heart potassium channels associated with QTc prolongation and risk for torsades de pointes
At the heart, antipsychotics can block the delayed rectifier potassium current mediated by the ion channel KCNH2, which is encoded by the HERG. This effect appears to be associated in a dose-related manner with the prolongation of QTc and subsequent greater risk for torsade de pointes.
In vitro human and animal studies
In human embryonic kidney cells, half of the maximal concentration (called IC_{50}) for identifying binding to these potassium channels was 0.57 μM for paliperidone and 0.16 μM for risperidone, indicating that both are likely to increase QTc in a concentration-dependent manner, but risperidone is between 3 to 4 times more potent (0.57/0.16=3.6) than paliperidone [11].
Animal studies also suggest that paliperidone increases QTc in a dose-dependent manner, although to a lower extent than risperidone [12-15].
Clinical data
1) Data comparing risperidone and 9-hydroxyrisperidone concentrations in risperidone patients: In normal metabolizers, 9-hydroxyrisperidone concentrations are approximately 4-5 times higher. This is why it is not surprising that two studies indicated that 9-hydroxyrisperidone concentrations may be more important than risperidone concentrations for predicting prolonged QTc in risperidone patients [16, 17].
2) Data comparing patients taking risperidone or paliperidone: • Meta-analytical evidence describing one paliperidone and five risperidone RCTs suggest a small increase in QTc for risperidone, while paliperidone was no different than placebo [9] • There are several case reports with risperidone-related QTc prolongation and even torsades de pointes [18], while those with paliperidone described no torsades de pointes [19-23] and only one case with QTc prolongation [24]. Although we could not identify any published case of torsades de pointes, in a paliperidone review Citrome emphasized that one case was described in the US package insert [10].

HERG: human ether-a-go-go–related gene; QTc: corrected QT interval

Supplementary Box S2. Limitations in the field (1-4) and in this article (5).

1. Lack of understanding of the possibility of low bioavailability of the oral ER formulation

Although we do not understand very well the causes and their relevance in the clinical environment, our review of the limited pharmacokinetic data provided by the marketer indicates that the standard oral paliperidone ER formulation may have very low bioavailability (28%).

2. Lack of blinding in the design

Meta-analyses of RCTs particularly emphasize blinding as a way of avoiding the risk of bias. Lack of blinding is not much of a risk for this combined analysis of TDM studies since the analyzed TDM data are unlikely to be affected by biases from the original investigators due to:

- First: the inherent blinding in the TDM analyses. Blinding in TDM is introduced by the fact that clinicians send blood samples to a laboratory that assumes patient compliance, although the lab can never be sure. Furthermore, the TDM laboratory performs the analyses using chemical methods and mathematical estimations which are relatively independent of human judgment.
- Second: blinding toward future application of the TDM data in our combined analysis which computes TDM ratios [1]. The ratios used in Tables 2 and 3 were estimated in terms of the current analysis based on extracted data from published manuscripts, of which it was not known they would be used in our calculations. When data was available, we estimated the total C/D ratios for paliperidone, since the original articles did not provide these ratios.

3. Reliance on company data and dearth of independent studies

- In our opinion, the major limitation of this review derives from the overrepresentation of the data from marketer-supported studies in the total existing pharmacokinetic data (14/23 studies).
- Moreover, the use of single-dose studies to assess DDI, renal and hepatic impairment by the marketer appears particularly worrisome. The best example is the valproate DDI study that completed but did not describe repeated paliperidone dosing data. The single-dosing data indicated that valproate increased bioavailability (or decreased clearance) by 1.52, while the only piece of data provided suggested that repeated dosage was associated with low paliperidone C/D ratio of 3.29 ng/ml, compatible with decreased bioavailability (or increased clearance). This second low C/D would be compatible with valproate being a paliperidone inducer. The most reasonable way to interpret these confusing results from this study is that valproate may first behave as a competitive inhibitor, and later as an inducer of paliperidone.

4. Pharmacokinetic limitations

Tables 1-5 assess the quality of the included studies based on a series of criteria such as:

- steady state
- personal variables (aging, renal and hepatic impairment)
- concomitant medications with inhibiting or inducing properties

The tables suggest that we have very limited understanding and data on how confounders influence steady-state paliperidone C/D ratio. Moreover, the limited number of DDI studies of paliperidone is dramatically insufficient, considering that polypharmacy may be the norm in paliperidone patients and paliperidone has been marketed by the company as having no or limited DDIs [40].

5. Limited combined analysis estimations and recommendations

Using this limited data we have provided limited:

- mean estimations by TDM combined analyses or estimations from single-dose studies that will require updating as new studies are published, and
- recommendations, which will require updating as new and hopefully better TDM studies are published.

C/D: concentration-to-dose ratios; DDI: drug-drug interactions; ER: extended-release; TDM: therapeutic drug monitoring.