Understanding the Pharmacodynamic and Pharmacokinetic Differences of Various Newer Antipsychotics

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INTRODUCTION

There are substantial differences in the pharmacodynamics and pharmacokinetics of newer antipsychotic medications which affect drug selection and treatment outcome for different patients.

METHOD

Pharmacodynamic and pharmacokinetic data was obtained from the drug development work done on each antipsychotic by their respective manufacturer and filed with the FDA as part of the approval process. An exhaustive review was done of the efficacy trials done with the antipsychotic, lurasidone, to illustrate what is required by the FDA for antipsychotic drug approval.

RESULTS

The dissimilarities in the receptor binding affinities and pharmacokinetics amongst these drugs are presented in tabular form. The pharmacokinetic differences include: their half-lives and metabolism including whether or not they undergo oxidative drug metabolism (phase 1) or simply conjugation reactions (phase 2).

Pharmacokinetic parameters for newer antipsychotics

Antipsychotic	Date of approval	Bio-availability	Food effect	Half- life t1/2 (hours)	Principal metabolizing enzyme(s)	Substantial CYP enzyme inhibition	If strong CYP inhibitor co-prescribed:	Dose adjustment as a result of impairment: Renal	Hepatic
Aripiprazole	2002	87%	none	75/146c	CYP 2D6 ≥ CYP 3A4	AUC ↑70% AUC ↑110%	Dose ↓ 50% Dose ↓ 50% Both: dose ↓ 75%	No	No
Asenapine	2009	35% vs 2%	< 20%g	24	UGT 1A4h >> CYP 1A2	AUC ↑ 29%	Caution	No	Not recommended
Clozapine	1989	70%	none	12	CYP 1A2	AUC ↑ 300%k	Caution, ↓ dose	No data caution	No data caution
Iloperidone	2009	96%	none	18/33	CYP 2D6 ≥ CYP 3A4	AUC ↑ 57% AUC ↑ 60% AUC ↑ 40%	Dose ↓ 50% Dose ↓ 50% Dose ↓ 50%	No	Not recommended
Lurasidone	2010	10%–20%	AUC ↑ 200% Cmax > 300%	18	CYP 3A4	AUC ↑ 900%	Contraindicated	Yes	Yes
Olanzapine	1996	60%	none	30	CYP 1A2	↑52% nonsmokers ↑108% smokers	Dose ↓	No	No
Paliperidone	2006	28%	AUC ↑ 50%	18	NA	AUC ↑ 50%	Dose ↓	Yes	No
Quetiapine	1997	Not specified	AUC ↑ 15%	6	CYP 3A4	Cmax ↑ 335%	Caution, dose ↓	No	Yes
Risperidone	1993	70%	none	3/20	CYP 2D6	AUC ↑ 300%–900%m dosey	Re-evaluate	Yes	Yes
Ziprasidone	2001	30%–60%	AUC ↑ 200%	7	Aldehyde oxidase >> CYP 3A4	AUC ↑ 35%l	No adjustment	No	No

Binding affinity of selected antipsychotic for specific neuroreceptors

Antipsychotic	Neuroreceptors D_2	5-HT_{2A}	5HT2C	α_1	H_1	M_1
Aripiprazole	0.34	3.4	15	57	61	>1,000
Asenapine	1.3	0.07	0.03	1.2	1.0	>1000
Clozapine	160	5.4	9.4	1.6	1.1	6.2
Haloperidol	0.7	45	NA	6	440	>1,500
Iloperidone	6.3	5.6	NA	0.36	473	>1,000
Olanzapine	NA	4	11	19	7	73
Paliperidone	3.40	1.14	NA	10	14	>1,000
Quetiapine	626	38	NA	14.6	4.41	1086
Risperidone	4	0.5	NA	0.7	20	>10,000
Ziprasidone	4.8	0.4	1.3	10	47	>1,000
Lurasidone	1	0.5	NA	47.9	>1,000	>1,000

Data represented as K_i (nM)

Lurasidone pivotal trials in adult patient with schizophrenia

- Placebo-controlled trials (3 studies): Administration of fixed doses of lurasidone showed that lurasidone was superior to placebo on the Brief Psychiatric Rating Scale derived (BPRSd) total score and the Clinical Global Impression Scale (CGI-S).
- Placebo- and Active-controlled trials (2 studies): 2 fixed doses of lurasidone and an active control, olanzapine and quetiapine extended-release, to assess assay sensitivity. Both lurasidone doses and the active control at endpoint were superior to placebo on the Positive And Negative Syndrome Score (PANSS) total score and the CGI-S.
- Placebo and Active-control trial (1 study): 3 fixed doses of lurasidone and an active control, haloperidol to assess assay sensitivity. None of the treatments separated from placebo and hence this study was considered a "failed" trial.
- Active control trials (2 studies): one fixed dose of lurasidone and an active control, ziprasidone and risperidone. Both results were not statistically different in terms of reduction in PANSS score.

CONCLUSION:

There are substantial differences amongst the newer antipsychotics in terms of their pharmacodynamics and pharmacokinetics, which are relevant to drug selection.