

Essentials of Pharmacotherapy in the PD Patient, An Update

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Caveats

- No medication has FDA approval for the treatment of Personality Disorder
- All use of medications discussed in this presentation represent “off label” uses
- Studies must control for Axis I
- Pharmacotx in PD is symptom specific, i.e cognitive-perceptual, affective, impulsive-behavioral sx's.

Neuroleptic trials prior to 2000

- **EVIDENCE:** Inpt, Outpt. Adult, Adolescent
- **BPD, SPD**
- **RCTs (mean dose/qd):** Trifluoperazine (4.8mg), thiothixene (9.4mg), haloperidol (4.8mg), flupenthixol (20 mg inj q 4 wk),
- **Parallel comparisons:** loxapine (14.5mg) vs. chlorpromazine (110 mg), thiothixene (9.4mg) vs haloperidol (3mg).
- **Open label/Case reports:** thioridazine, flupenthixol, clozapine, olanzepine, risperidone

Neuroleptics (prior to 2000)

- 1st.gen NPs :low doses,weeks not months.
- Broad spectrum of effects: diminishes global symptom severity in all domains.
- More selective against cognitive-perceptual sxS: e.g. ideas of reference, paranoid ideation, illusions
- Also anger-hostility, impulsive aggression

Neuroleptic Update (>2000) (Second Generation NPs)

- Risperidone:
 - Koenigsberg (2003) SPD, RCT, 9 wks. 2 mg/qd (Risp>Plc: psychoticism, neg and pos sxs)
- Olanzapine:
 - *Zanarini et.al.(2001) BPD RCT 6 mo. 5.33 mg/qd. (OLZ>Plc in anger, hostility, paranoid, interpersonal sens, dissoc.sxs (SCL90); psychoticism; global fx .

- Bogenschutz et.al (2001) BPD RCT 12wk (2.5-20mg/day). (OLZ>Plc in global fx)
- Keshavan et.al. (2004) SPD open label 26 wks 9.32mg/day; (impr in: psychoticism (BPRS), depr (BDI,HamD), imp-agg (OAS), global fx (GAS))
- *Zanarini et.al.(2004) BPD Olz. (3.3mg) vs. Fluox.(15mg) vs. Olz(3.2mg)+ Fluox(12.7mg) combination; 8 wk.; (Olz, Olz+Fluox .combo.> Fluox in: depr, imp-aggression (OAS-m)).
Olz > Olz+Fluox on depression(MADRS))

- Olanzapine (cont.)

- Soler et.al.(2005) BPD RCT; DBT +Olz vs. DBT + Plc 8.83 mg/qd; 12 wk. Olz>Plc on depr, anx, imp-agg.
- *Zanarini et.al.(2007) BPD RCT 12 wk dose finding: Olz 2.5mg/day, Olz 5-10mg/day, Plc. Large N (451), Eli Lilly multicenter. Olz 5-10mg> Olz 2.5mg. and Plc on ZAN-BPD (e.g. categorical defn, DSM IV criteria quantified).

- *Schultz et.al.(2008) BPD RCT 12 wk. 7.09 mg/day. Large N (314) Eli Lilly multicenter, 52 sites. (No diffs in overall ZAN-BPD chg (categorical defn), but Olz>Plc in dimensions: Intense Anger (ZAN), irritability (OAS-M), hostility (SCL90)).
- Aripiprizole
 - Nickel et.al.(2006) BPD RCT 8wks 15mg/day; (Ari >Plc in: all SCL90 scales, HamD, Ham-A, 4 anger scales (STAXI))

- Quetiapine (all Open Label)
 - Villeneuve et.al.(2005) BPD 12 wk 251 mg/qd.(impr: imp.,hos.,depr, anx.,global)
 - Bellino et.al.(2006) BPD 12 wk 309 mg/qd;(impr: BPRS,HamA, global(CGI), impulsivity)
 - Perrella et.al. (2007)BPD 12 wk. 540 mg/qd; (impr: HamD, BPRS hos, suspic, global fx (CGI,GAF), aggression)

NEUROLEPTIC UPDATE: ESSENTIALS

Indications in PD:

Psychoticism (referential thinking, paranoid ideation, illusions); Anger-hostility, impulsive aggression; Acute symptom severity across all domains, a non-specific effect

Strategies: Low doses, short durations (wks)

Limitations: 1st. gen.: more side effects; poorly tolerated in continuation. 2nd. gen.: similar benefits, more favorable side effect profiles. Effects are modest, and broad spectrum.

ANTIDEPRESSANTS (prior to 2000): SSRI/SNRI

- EVIDENCE: Inpatient, Outpatient
- BPD, impulsive aggression in diverse PDs
- RCTS: fluoxetine (3 studies; 12 wk, 14 wk. 20-80 mg.)
- Open Label: fluoxetine (to 80 mg), sertraline (to 200 mg), venlafaxine (to 400 mg);
- Efficacy against depression, anxiety, impulsive aggression, irritability. Improvement in impulsive aggression indep. of change in depr or anx.

TCA AND HETEROCYCLICS

- EVIDENCE: Inpatient, Outpatient
- BPD, SPD, BPD/Histrionic suicide attempters
- RCTs: amitriptyline, imipramine, desipramine, amoxapine, imipramine, mianserin,
- Amitriptyline: impr. in depr., indirect hos. in BPD; Behavioral toxicity with Ami in BPD inpts,
- Desipramine: no diff from Plc in BPD;
- Amoxapine : effect only in BPD with comorbid SPD.

MAOIS (prior to 2000)

- EVIDENCE: Inpatient, Outpatient
- BPD as primary dx, BPD with hysteroid dysphoria, atypical depression with BPD.
- 3 RCTs: tranylcypromine, phenelzine (2)
- 5-6 wk dur. 1 continuation of 16wks (phen)
- MAOIs > Plc on mood sxs and impulsivity;
- anger-hostility at 5-6wks; depression and irritability at 16 wks. Effects indep of Axis I

ANTIDEPRESSANT UPDATE (>2000)

- Fluvoxamine
 - Rinne (2002) female BPD RCT 150 mg/qd; 6 wks, then 12 wks all on fluox. (impr. mood shifts, not anger/impulsivity).
- Citalopram
 - Reist (2003) ClusterB/IED Open 45.5 mg/qd; 8 wks. (impr: irritability, aggression)

- Fluoxetine

- Zannarini et.al. (2004) BPD 3 meds, Fluox (15mg) vs Olz (3.3mg) vs Olz (3.2 mg)+Fluox (12.7mg); 8 wk. (impr. with Fluox. on depression and imp/agg.)
- *Simpson et.al (2004) BPD, acutely admitted to 5 day partial pgm. RCT: DBT + Fluox.(to 40 mg/qd) vs. DBT+Plc.; 12 wk. NO ADVANTAGE FOR FLUOX . OVER PLC. Within group: DBT+Plc (impr on depr/global fx.); DBT + fluox.(no signif impr. but fluox group more impaired at start.) No control for time alone.

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Antidepressant Update: Essentials

Indications in PD: Subjective depressed mood (efficacy may be indep. of Axis I); MAOIs: atypical depression, “Hysteroid Dysphoria,”

Impulsivity in the context of affective dysregulation

Strategies/limitations: SSRI preferred, MAOIs also effective, avoid TCAs (behavioral toxicity). Full doses, long durations (months). DBT may be sufficient for acute sx's.

SSRI safest in overdose. Compliance issues with MAOIs.

LITHIUM/ ANTICONVULSANTS

(prior to 2000)

- EVIDENCE: Inpat., Outpt.,. Adult, Adolescent
- ASPD, assaultive prisoners, delinquents, BPD, impulsive PDs (IED)
- RCTs: lithium (BPD).
- RCTS: phenytoin (ASPD) , carbamazepine (BPD), divalproex sodium (BPD)
- OPEN LABEL/case reports: divalproex, lamotrigine

- Decreased impulsivity in BPD on Lithium, trends for less anger, suicidal sx's (vs. plc, desip) (Links et.al.1990)
- Decreased impulsive-agg in ASPD on Phenytoin (Barratt et.al.1997)
- Decreased behavioral dyscontrol, impulsivity, suicidality in BPD, on Carbamazepine , improvement in anxiety,anger, euphoria (Cowdry and Gardiner,1988)
- Decreased agitation, anger, impulsive-aggression, irritability, mood instability, impulsivity, anxiety on Divalproex Sodium (Wilcox, 1995, Stein et.al.1995, Kavoussi & Coccaro,1998)

Anti-Convulsants > 2000

- Divalproex Sodium

- Frankenburg & Zanarini (2002) female BPD+**BPII** RCT 8 wk. 850 mg/qd (Dival>Plc on interpersonal sensitivity, anger/hostility (SCL90), impulsive-aggression (OAS-M).
- *Hollander (2001) BPD outpt (**no Axis I dep or BP**) RCT 10 wks (**no Plc completers**, dival: impr global fx (CGI).
- *Hollander (2003) Cluster B 12 wks; RCT; (impr. Irr, agg. (2005): BPD only; impr.in agg, imp, affective instability, depr, hypomania)
- High pretx agg/ imp. predict best response.

Anti-Convulsants > 2000 (cont.)

- Oxcarbamazepine
 - Bellino et.al. (2005) BPD open label; 12 wks; 1200-1500mg/qd.(impr: global fx, BPRS total, anxiety, imp, aff. instab., interpersonal rels, anger.)
- Lamotrigine
 - *Tritt et.al.(2005) BPD female RCT 8 wks; 200 mg/qd; (LTG>Plc on anger scales (STAXI))

Anti-convulsants > 2000 (cont.)

- Topirimate
 - *Nickel et.al.(2004/2005) BPD female/male RCT 8 wks.(to 250 mg/qd); (TOP>Plc on 4 anger scales (STAXI).
 - *Loew et.al. (2006) BPD female RCT 10 wks (to 200mg/qd) (TOP> Plc on SCL90:Somatization, Interpersonal Sens, Anx, Hos, PhoAnx,Global Severity; quality of life, interpersonal problems

ANTICONVULSANTS/LITHIUM: Essentials

Indications:

Behavioral impulsivity, impulsive-aggression, assaultiveness, mood lability; Anger

Strategies: lithium, divalproex sodium, carbamazepine, (oxcarbamazepine); For anger: topiramate , lamotrigine. Full doses with plasma level controls as appropriate.

Long duration (Months)

Limitations: Overdose risk (esp. Lithium); blood draws, non-compliance.

ANXIOLYTICS: ESSENTIALS

EVIDENCE: Inadequate database in PD. 1 RCT:
BPD outpatients; Cowdry (1986) 4 drug+plc
crossover (alprazolam), some case reports .

Limitations: RCT reported behavioral dyscontrol in
outpatients with BPD on alprazolam.

Case reports suggest longer half-life drug (e.g.
clonazepam) may be useful for anger/agitation,
anxiety.

Potential for abuse.

CONCLUSIONS

- I. More studies needed. The Database is woefully inadequate.
 - Drugs have a broad spectrum of efficacy
- II. Studies with shared methods are needed to facilitate meta-analyses
- III. Psychotherapies powerfully affect response
- IV. Drug effects are modest.
- V. Medication does not cure character**