California Department of State Hospitals
Clinical Operations Division

PRN
Psychopharmacology Resource Network

DEPARTMENT OF STATE HOSPITALS
PRN Vision

Enhancing the California Department of State Hospitals’ psychopharmacology practices through consultation, education, policy change, and outcomes research.
Left to Right
Jonathan Meyer, M.D. (Covers all 5 Hospitals)
George Proctor, M.D. (DSH-Patton)
Stephen Stahl, M.D., Ph.D. (Academic Advisor)
Eric Schwartz, M.D. (DSH-Napa)
Michael Cummings, M.D. (DSH-Patton)
Jennifer O’Day, M.D. (DSH-Metropolitan)
PRN Group: Publications


PRN Group: Publications

- Cummings M. The Neurobiology of Psychopathy: Recent Developments and New Directions in Research and Treatment. CNS Spectr 2015 Jun; 20(3): 200-6
PRN Group: Publications


PRN Group: Publications


P.R.N.

• The initials of our group are a play on the common prescription term “PRN”

• From the Latin: Pro Re Nata = as the need/situation arises.

• That’s what we do: provide our resources as needed.
PRN: How It Works

• We strive to be considered a resource that clinicians seek out; not a supervisory tool

• Clinical teams should be happy to see us and hospital managers should like our results

• Offer multiple points to interface with clinicians and administrators regarding psychopharmacology practice and evidence
PRN: How It Works

- Consultations
- Conference calls
- Committees
- Lectures
- Research and Publications
- Literature searches
- Mentoring

“Anything you need that we can do, we will provide it.”

-PRN member
Consultations

• “Ms. X has had continued paranoia and resulting violence despite polypharmacy.”
  – Adequate trials at adequate levels? Might need clozapine…

• “Mr. A has low ANC and WBC. Should I switch the antipsychotic?”
  – Have the ANC/WBC been low on and off medications? Might be BEN…

• “Ms. D is still psychotic despite taking Zyprexa for 7 months.”
  – What have the Zyprexa levels been?…

• “Mr. S reports side effects from all medications except he had a good response to Lexapro and Ritalin in the past. Please make medication recommendations.”
  – What are the symptoms being treated? What were the descriptions of side effects?…
Consultations

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<td>3081</td>
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*Data for 2018 = Jan through April*
PRN: How It Works

- Consultations
- Conference calls
- Committees
- Lectures
- Research and Publications
- Literature searches
- Mentoring

Convey the same principle using each method: e.g. Drug levels
PRN: How It Works

- Consultations – drug levels
- Conference calls – drug levels
- Committees – drug levels
- Lectures – drug levels
- Research and Publications – drug levels
- Literature searches – drug levels
- Mentoring – drug levels
PRN: How It Works

- Special Appearances - Having Dr. Stahl and the DSH Medical Director visit a hospital and discuss difficult cases

Tremendous increase in consultation requests
PRN: How It Works

• We enhance knowledge and ability to care for patients
  – Questions and problems are our lifeblood
  – The same question 5X from the same practitioner should result in supportive and patient responses from us
PRN: How It Works

• Quality is continually improving by:
  – Consulting each other regularly on cases/articles
  – PRN supervisor ensures organized forward progress
  – Every consult is shared with all PRN members, allowing feedback
A Starting Point

STOP-A

Selected Treatment Of Psychomotor-Agitation

Psychopharmacological Management of Acute Violence
What is STOP-A?

- High number of violent incidents occur **shortly after admission**
- Disproportionately **large number of incidents** are caused by a relatively **small number of individuals** prone to psychomotor agitation
- **STOP-A** is a pharmacological **algorithm** designed to hasten stabilization of targeted individuals
Where Did STOP-A Come From?

- Developed by Michael Cummings, M.D., PRN Consultant at DSH-Patton
- Supported by multiple references and empirical experiences within DSH
- STOP-A is included in the DSH Psychotropic Medication Policy
Psychopharmacological treatment assists the individual in becoming mentally available for additional forms of psychosocial treatment.
Cal-VAT Guidelines

California State Hospitals Violence Assessment and Treatment

What are Cal-VAT Guidelines?

A published set of comprehensive guidelines for the assessment and treatment of violence/aggression of various etiologies including:

- **Psychotic** aggression and **impulsive** aggression—often related to schizophrenia, mood disorders, ADHD, trauma, etc.
- **Predatory** aggression—often associated with psychopathy and other personality disorders.
Where Did Cal-VAT Come From?

Developed from UC Davis research*, a comprehensive review of the literature, clinical trial results, and years of clinical experience in treating patients who are persistently violent or aggressive in the California DSH

Cal-VAT Overview and Key Points

- Determine type of aggression (psychotic, impulsive, predatory) as well as environmental factors that may exacerbate aggressive behaviors
- Actively monitor therapeutic drug levels during treatment
- Strongly consider using high dose/plasma level antipsychotic monotherapy or antipsychotic polypharmacy in patients who are aggressive and violent

Stahl SM et al. (2014). California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. CNS Spectrums, 19, pp 449-465
Cal-VAT Overview and Key Points

• Strongly consider clozapine for patients with persistent aggression
• Actively monitor for and treat comorbid conditions that may contribute to aggressive behavior, including substance abuse
• Continually evaluate patients using violence risk assessment tools
• Integrate psychosocial therapies into the treatment plan for patients who are chronically aggressive

Stahl SM et al. (2014). California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. CNS Spectrums, 19, pp 449-465
Evaluate patient for causes of aggression

• Aggression type
  – Psychotic
    – Often noted to be “unprovoked”
    – Patient misunderstands or misinterprets environmental stimuli
    – Attributable to positive symptoms of psychosis
      » Paranoid delusions of threat or persecution
      » Command hallucinations
      » Grandiosity
  Accompanied by autonomic arousal
Cal-VAT Guidelines

Evaluate patient for causes of aggression

• Aggression type
  – Impulsive
    – Often provoked
    – Hyper-reactivity to stimuli
    – Emotional hypersensitivity
    – Exaggerated threat perception
    – Involves no planning
    – Accompanied by autonomic arousal
  – Predatory
    – Planned assaults
    – Goal-directed
    – Lack of remorse
    – Autonomic arousal absent

Stahl SM et al. (2014). California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. CNS Spectrums, 19, pp 449-465
Psychotic aggression is the direct result of poorly controlled positive symptoms of psychosis.

Although it is the least frequent form of aggression (15%), it is the **most treatable**.

In general, treatment of psychotic aggression will follow treatment pathways for schizophrenia non-responders.

What Works for Psychosis?

1. Antipsychotics
2. Antipsychotics
3. Antipsychotics
Inadequate Antipsychotic Treatment Response?

- Question #1 - Do you have the correct diagnosis?
- Question #2 – Is the aggression driven by psychosis?
- Question #3 - Has the patient received an adequate trial of drug treatment?
Inadequate Antipsychotic Treatment Response

Adequate Drug Trial but No Response Or Adverse Effects

Obtain another Plasma Drug Level
Medication Plasma Levels

• Plasma level is the best proxy we have for antipsychotic brain activity

• For those on oral medications dose is a poor predictor of plasma level due to adherence and kinetic issues
  – The decision to terminate a medication trial is best made by consideration of response and tolerability, informed by the levels.
  – Obtaining plasma levels during periods of stability, especially in controlled circumstances, can help detect nonadherence
  – A working knowledge of dose-plasma level relationships for oral and depot medications can also help detect kinetic issues (e.g. CYP 2D6 ultrarapid metabolizers)

• For nonresponders, levels can help determine whether a point of futility has been reached, or whether further dose (and level) increases can be useful

• Laboratory reference ranges are idiosyncratic at best
  – Minimum response thresholds tend to be relatively accurate
  – The upper limits are based on average tolerability. Your patient may not be average and may both require and tolerate a higher plasma level.
Inadequate Treatment Response: Checking Plasma Drug Levels

When checking plasma antipsychotic drug levels....

1. Does the plasma drug level correspond to the dose being administered?
2. Is the plasma level above the minimum and below maximum?
3. Is the patient experiencing dose-limiting adverse effects or has the plasma level exceeded the point of futility?
Drug Min-Max Levels

Aripiprazole 150 - 500 ng/ml
Clozapine 350 - 1000 ng/ml
Fluphenazine 0.8 - 4.0 ng/ml
Haloperidol 5 - 30 ng/ml
Olanzapine 40 - 200 ng/ml

Inadequate Treatment Response: 
Low Antipsychotic Plasma Level

Plasma Drug Level **Below** minimum

Steps to Optimize Adherence

Possible Pharmacokinetic Failure

High Dose Antipsychotic Monotherapy

Stahl SM et al. (2014). California State Hospital Violence Assessment and Treatment (Cal-VAT) guidelines. CNS Spectrums, 19, pp 449-465
Inadequate Treatment Response: Antipsychotic Plasma Level Above Minimum

- **Plasma Drug Level Above Min.**
  - Adverse effects present: **SWITCH**
  - Adverse effects (AE) absent: Push level to point of AEs or futility before deciding patient is a pharmacodynamic failure
The Point of Futility

- Historical Rule: Titrate antipsychotic to EPS and then reduce dose
- For a small subset of patients the EPS threshold may never be reached.
- Probably a point of futility for most antipsychotics beyond which the likelihood of response is virtually nil:
  - Haloperidol > 30 ng/mL
  - Fluphenazine > 4.0 ng/mL
  - Olanzapine > 200 ng/mL
Inadequate Treatment Response: Antipsychotic and No Adverse Effects

Options:
1. Higher dose of atypical antipsychotic with substantial $D_2$ blockade
2. Switch to a first generation antipsychotic for more $D_2$ antagonism
3. If local regulations limit maximal doses, clozapine is the next step
Treatment Resistance: Clozapine

- Antipsychotic of choice for treatment refractory schizophrenia
- **Response rates up to 60%**
- Minimum therapeutic threshold is a plasma level of 350 ng/mL
  - Levels up to 1000 ng/ml may be needed (if tolerated) for adequate response in some patients

Antipsychotics for Violent Patients with Schizophrenia:

A Randomized, Double-Blind, Parallel-Group, 12-Week Trial

- Physically assaultive inpatients with schizophrenia or SAD in NY state psychiatric facilities were randomly assigned to treatment with clozapine (n=37), olanzapine (n=37), or haloperidol (n=36)

- Mean doses at week 12:
  - Clozapine: $565.5 \pm 112.7$ mg
  - Olanzapine: $24.7 \pm 6.1$ mg
  - Haloperidol: $23.3 \pm 7.1$ mg

Clozapine and Impulsive Violence in Psychosis: Results

- PANSS scores showed no significant differences across groups
- Clozapine produced significantly better reductions in:
  - MOAS* verbal aggression scores
  - MOAS physical aggression scores
  - MOAS total aggression scores

*Modified Overt Aggression Scale

How Does Clozapine Decrease Violence?

- We know that reducing psychosis decreases psychotic violence.
- Krakowski and colleagues also found that clozapine has anti-aggressive properties independent of its antipsychotic effects.
- These effects are due to improved executive functioning (prefrontal cortex).

Clozapine Use in DSH

• An increase of >100% over 5 years!

Perspective

• California DSH Clozapine use = 12.4%
• NY State Hospitals Clozapine use = 53.1%
  – John Kane and Hillside Hospital
  – Resident trainees familiarity with Clozapine
  – Willingness to support reluctant patients

• A lot of room for improvement
Impact of Psychopharmacology Consultation on Violence

Analysis of violence outcomes after psychopharmacology consultations at one state hospital in California from 2014-2017 (Patton State Hospital).

Inclusion criteria for the analysis:

a. There was at least one incident of violence in the 90 days prior to the psychopharmacology consultation.

b. The patient was at the hospital ≥ 60 days after the consultation:
   
   i. To allow sufficient time for interventions to succeed

   ii. To remove the confounding effect of violent patients that are discharged back to court shortly after the consultation (typically those without involuntary medication orders in need of a court hearing)
Impact of Psychopharmacology Consultation on Violence Rates

Results:

Sample size: 226 consultations met the above criteria

Mean 90 day rate of aggression prior to consultation: \(5.45 \pm 7.98\)
Mean 90 day rate of aggression after the consultation: \(1.39 \pm 2.71\)

This difference in the 90 day aggression rate represented a 74.5% reduction, and was highly significant (p < .001).

Limitation: the lack of a control group
PRN Vision

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Questions?

Eric Schwartz, M.D.
DSH- Napa
707-253-5259
eric.schwartz@dsh.ca.gov

George Proctor, M.D.
DSH- Patton
909-425-7471
george.proctor@dsh.ca.gov