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Taming the Aftermath: Practical Approaches to Postictal Behavioral Management

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BACKGROUND

- Effective management of postictal agitation (PIA) is important given that the episodic changes in behavior and cognition may be more nuanced than agitation in other conditions or primary psychiatric disorders
- While no clear evidence-based guidelines exist for the treatment of PIA, consensus statements for pharmacotherapy have been reviewed by authors who describe several approaches and considerations:[1-3]
  - Selection of antipsychotics with a low risk of seizure exacerbation or induction
  - Drug-drug interactions between commonly used antipsychotics and antiepileptics
  - Role of benzodiazepines with or without antipsychotics for managing PIA
- There is limited guidance with treatment strategies for PIA management in epilepsy monitoring units (EMU) using agents with minimal effect on EEG activity
- There is limited guidance on longitudinal management of PIA in the outpatient setting in the context of:
  - Potential role of long-acting injectable antipsychotics (LAIA)
  - Comprehensive list of drug-drug interactions between benzodiazepines, antipsychotics, and antiepileptics for appropriate treatment selection

OBJECTIVES

The aim is to devise three David Osser-styled algorithms for the management of PIA in three distinct settings to help consult-liaison psychiatrists with appropriate treatment decision-making:

- Epilepsy monitoring unit (EMU)
- Non-EMU acute care areas
- Ambulatory clinics

METHODS

Systematic electronic search was performed for records indexed within MEDLINE, EMBASE, and the Cochrane database between 2000 and 2023 to identify articles on PIA management and we identified three clinical settings which may benefit from unique and standardized pharmacological approaches

RESULTS

Epilepsy Monitoring Unit: PIA Order Set

Medications with low risk for affecting EEG activity and low risk for seizure occurrence	
Mild Agitation	Risperidone ODT
Moderate Agitation	Haldol Lactate IM or IV
Severe Agitation	Droperidol IM

ODT: orally-disintegrating tablet; IM: intramuscular; IV: intravenous

- Ziprasidone would be recommended for use as an alternative agent if extrapyramidal reactions occur with droperidol or haloperidol, since anticholinergics are generally avoided due to effects on EEG
- Benzodiazepines were not recommended as they may mask electrical activity of EEG monitoring

- Standardized order set with two sections to choose from: **low risk** vs **high risk**
  - Selection between either risk section is based on age (<65 or 65+) and relevant QTc-prolonging risk factors, given the use of haloperidol and droperidol
  - **Low** risk dosing:
    - Haloperidol 5-10 mg q4hrs PRN
    - Droperidol 5-10 mg q4hrs PRN
  - **High** risk dosing:
    - Haloperidol 2.5-5 mg q4hrs PRN
    - Droperidol 2.5-5 mg q4hrs PRN
- Risperidone dosing is same for both risk sections: 1-2 mg oral q4hrs PRN
- Of the remaining agitation medications available, it was recommended to avoid using olanzapine due to its risk of altering EEG activity and avoid using chlorpromazine given its seizure-exacerbating risks
- Fluphenazine was not recommended because due to its vial size must be drawn up in the IV room of our main pharmacy and is not feasible for administration during acute agitation as well as already working similarly to both 1st gen agents

Non-EMU Acute Care PIA Order Set

Non-EMU acute care areas do not have restrictions on use of benzodiazepines or agents which can alter EEG activity as EEG monitoring is not routinely occurring. Also, most individuals with epileptic histories are already typically on antiepileptic agents which would provide protection against seizures. As such, our institution has devised an order set which would delineate the use of specific medications which could apply to PIA and non-PIA types:

Agitation due to delirium or known psychotic history	Olanzapine 5 mg ODT q6hrs PRN – mild agitation Olanzapine 10 mg ODT q6hrs PRN – moderate agitation Olanzapine 10 mg IM q6hrs PRN – severe agitation
Agitation due to substance or undifferentiated	Lorazepam 2 mg PO q8hrs PRN – mild agitation Midazolam 5 mg IM or Lorazepam 2 mg IM q6hrs PRN – moderate agitation Midazolam or Lorazepam with Haloperidol 5 mg IM q6hrs PRN – severe agitation

Ambulatory PIA Algorithm

Antiepileptic CYP Inducers	
3A4	(Moderate – Strong): carbamazepine, phenobarbital, phenytoin, primidone (Moderate): eslicarbazepine, oxcarbazepine, cenobamate (Weak – Moderate): clobazam, rufinamide, topiramate
2C9	(Moderate): carbamazepine (Weak): phenobarbital, primidone, phenytoin
2B6	(Moderate): carbamazepine (Weak): cenobamate, phenobarbital, phenytoin, primidone
1A2	(Moderate): carbamazepine (Weak): phenobarbital, phenytoin, primidone
2A6	(Weak): phenobarbital, primidone, valproic acid

1st Generation Antipsychotic CYP Substrates	
3A4	(Major): haloperidol (Minor): chlorpromazine, loxapine, perphenazine
2D6	(Major): haloperidol, perphenazine (Minor): chlorpromazine, fluphenazine, loxapine
1A2	(Minor): chlorpromazine, haloperidol, loxapine, perphenazine
2C9/19	(Minor): perphenazine

Benzodiazepine CYP Substrates	
3A4	(Major): clobazam, clonazepam, diazepam, midazolam (Minor): clorazepate
2B6	(Minor): clobazam, diazepam, midazolam
2C19	(Major): clobazam, diazepam
1A2/2C9	(Minor): diazepam

- Lorazepam is not a CYP substrate

Antiepileptic CYP Inhibitors	
3A4	(Weak): cannabidiol, stiripentol, valproic acid
2C9	(Weak): cannabidiol, valproic acid
1A2	(Moderate): stiripentol (Weak): cannabidiol
2D6	(Moderate): clobazam, valproic acid
2C19	(Moderate): cannabidiol, cenobamate, stiripentol (Weak): felbamate, eslicarbazepine, valproic acid

Antiepileptics with minimal to no CYP effect	Brivaracetam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, perampanel, pregabalin, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide

2nd Generation Antipsychotic CYP Substrates	
3A4	(Major): aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, lumateperone, pimavanserin, quetiapine, risperidone, ziprasidone (Minor): paliperidone
2D6	(Major): aripiprazole, brexpiprazole, risperidone (Minor): cariprazine, clozapine, quetiapine, olanzapine, pimavanserin
1A2	(Major): clozapine, olanzapine (Minor): lumateperone, ziprasidone
2C9/19	(Minor): clozapine

Antipsychotics by Seizure-Inducing/Exacerbating Risk	
High Risk	Clozapine, chlorpromazine
Moderate Risk	Olanzapine (dose-dependent), Quetiapine (dose-dependent)
Low Risk	Aripiprazole, fluphenazine, droperidol, haloperidol, paliperidone, perphenazine, risperidone ziprasidone,

- Limited data available for risk of seizure with oral loxapine, brexpiprazole, cariprazine, lurasidone, lumateperone, and pimavanserin

RECOMMENDATIONS

EMU:

- Recommended to use EMU order set which incorporates rapid-acting medications with various routes of administration with low risk of affecting EEG activity and low risk for seizure exacerbation or seizure induction
- Avoid using benzodiazepines despite being agents used for PIA as they can affect EEG monitoring activity
- In setting of EPS with haloperidol or droperidol, can use ziprasidone as an alternative agent

Non-EMU:

- Non-EMU order set already incorporates a variety of medications which are safe to use in patients with epileptic histories and on anticonvulsants who have PIA

Ambulatory Clinics:

- Planned implementation of the ambulatory care algorithm in Memorial outpatient neurology clinics
- The algorithm uses the understanding of common CYP inducers and inhibitors alongside those antipsychotics and benzodiazepines which are CYP substrates to determine appropriate treatment options for longitudinal PIA management in the outpatient setting
- This algorithm allows healthcare prescribers to regulate the appropriateness of long-term PIA management by selecting antipsychotics and/or benzodiazepines most appropriate with the corresponding anticonvulsant used to prevent breakthrough PIA from occurring with CYP inducers and/or prevent medications used for PIA to have pronounced side/adverse effect profiles with accumulation by CYP inhibitors
- The algorithm also allows prescribers to pick from a wide variety of antipsychotics having low risk for seizure occurrence
  - Fluphenazine is a 1st-generation antipsychotic which has a long-acting injectable formulation and can be used for longitudinal PIA
  - Paliperidone is a 2nd-generation antipsychotic which has a long-acting injectable formulation and can be used for longitudinal PIA

DISCLOSURES

The authors of this presentation have no financial or personal conflicts of interest which may impact the results of the study

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