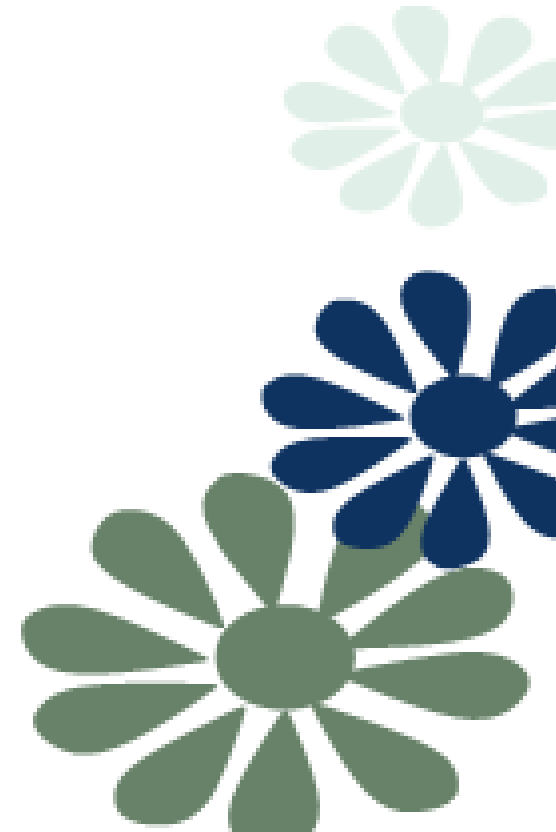


Pharmacological considerations for acute disturbance: Fundamentals of prevention and Clopixol acuphase[®]

James McCarthy

Clinical Pharmacy Manager - Inpatient Services

Devon Partnership NHS Trust



Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation

Psychopharm

Journal of Psychopharmacology
1-40

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Devon Partnership 
NHS Trust

Prescribing Guideline

Safe and Appropriate Use of
Clopixol Acuphase®
(Zuclopenthixol acetate)

PG21

NICE National Institute for
Health and Care Excellence

NICE

guideline

Violence and aggression: short-term management in mental health, health and community settings

NICE guideline

Published: 28 May 2015

www.nice.org.uk/guidance/ng10

FUNDAMENTAL PRINCIPLES

Multidisciplinary approach
Effective interventions
Proportionality of intervention
Treatment individualisation/choice
Treatment optimisation of underlying disorder

and

Continuous monitoring/review of:
Mental/physical health
Risks to self/others
Treatment effectiveness/harm
Patient engagement level

and

Consideration of modifiers:
Pregnancy
Drugs and alcohol
Medical frailty/physically compromised
Psychotropic naivety
Regularly prescribed psychotropics
Learning disability
(Extremes of) age

PRE-RT: DE-ESCALATION

Continual risk assessment (III,C)
Self-control techniques (IV,D)
Avoidance of provocation (IV,D)
Respect patient space (IV,D)
Management of environment (III,C)

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Re-framing events for patient (III,C)
Non-confrontational limit setting (III,C)

PRE-RT: ORAL/ORAL-INHALED/BUCCAL

Oral-Inhaled Loxapine (Ib,A)[†]
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Oral Promethazine (S)

or

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Oral Olanzapine (Ib,A)
Oral Quetiapine (III,C)
Oral Risperidone (Ib,A)

RT: INTRAMUSCULAR MONOTHERAPY

IM Lorazepam (Ib,A)[‡]

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IM Promethazine (Ia,D)

or

IM Aripiprazole (Ia,A)
IM Droperidol (Ib,A)^{*}
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RT: INTRAMUSCULAR COMBINATIONS

IM Promethazine PLUS IM Haloperidol (Ia,A)^{*}

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Senior advice (S)
Comprehensive case review (S)
Review appropriateness of clinical setting (S)
Consider Zuclopenthixol Acetate (III,C)^{*}
Consider ECT (IV,D)

KEY

- () evidence and recommendation
- † bronchodilator available
- * ECG
- ‡ flumazenil immediately available
- ^ avoid with IM benzodiazepines
- ◇ respiratory depression caution

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'Prevention is better than cure'

Erasmus. 16th century.



Optimise current treatment

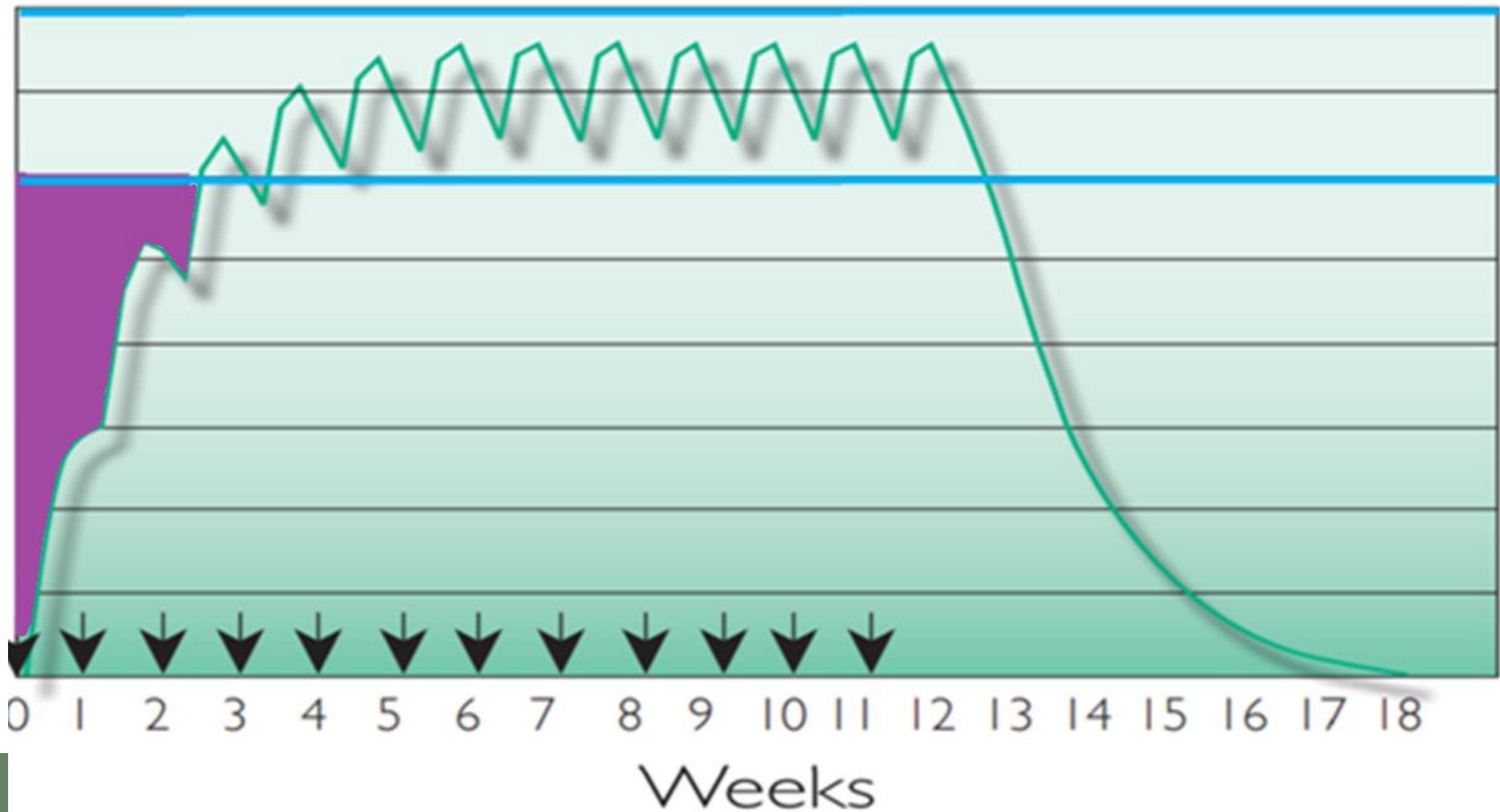


Offending agent(s)	Potential to cause/worsen/be confused with acute disturbance
Compliance	Intentional/non-intentional non-compliance
Unintentional medication/substance effects	Benzodiazepines – paradoxical effects (or not) Antidepressant – mania/switching Aripiprazole – agitation/alertness High doses/toxicity – confusion Illicit substances - psychosis
Interactions	Enzyme inducers
Withdrawal/discontinuation effects	Alcohol Opiates Benzodiazepines Antipsychotic - clozapine
Delayed treatment response	Time to reach peak plasma concentration and steady state Slow to increase dose where necessary Untimely plasma levels
Medication errors	Missed administration Incorrect dose/drug Wrong needle length

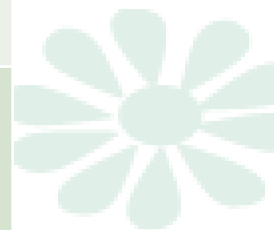


It's all about timing...





Drug	Pharmacokinetics	Initiation
Flupentixol decanoate	<ul style="list-style-type: none"> - Tmax 4-10 days - Half-life 21 days - Steady state 6-12 weeks 	- Test dose
Haloperidol decanoate	<ul style="list-style-type: none"> - Tmax 3-9 days - Half-life 21 days - Steady state 10-12 weeks 	- Test dose
Zuclopenthixol decanoate	<ul style="list-style-type: none"> - Tmax 3-7 days - Half-life 19 days - Steady state 10-12 weeks 	- Test dose
Aripiprazole monohydrate	<ul style="list-style-type: none"> - Tmax 4-7 days - Half-life 30-47 days - Steady state 16 weeks 	- Oral
Olanzapine pamoate monohydrate	<ul style="list-style-type: none"> - Tmax 2-6 days - Half-life 30 days - Steady state 12 weeks 	- Oral
Paliperidone palmitate (monthly)	<ul style="list-style-type: none"> - Tmax 13 days - Half-life 25-49 days - Steady state 9-21 weeks 	- Oral
Risperidone microspheres	<ul style="list-style-type: none"> - Tmax 30 days - Half-life 3-6 days - Steady state 6-8 weeks 	- Oral



What can we do while we wait?

- Watchful waiting?
 - Prescribe 'when required' RT and pre-RT just in case
- Combine with oral medication?
 - Potential for high dose antipsychotic – physical monitoring
 - Other pharmacological classes (e.g. benzodiazepines)
- Further restrictive interventions?
 - Short-acting IM injection if refusing regular oral
 - Potential for high dose antipsychotic under restraint – physical monitoring
 - Short-duration of action



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What is Clopixol acuphase[®]?

- Zuclopenthixol acetate
- *'Initial treatment of acute psychoses including mania and exacerbation of chronic psychoses, particularly where a duration of effect of 2-3 days is desirable'*
- Refusal of oral and limited benefit from repeated short-acting IM injections



Intervention (IM)	Lorazepam	Clopixol acuphase [®]	Clopixol depot
Onset of action	Tmax: ~15–30 mins Half-life: ~6-8 hours		Tmax: ~3-7 days Half-life: ~19 days

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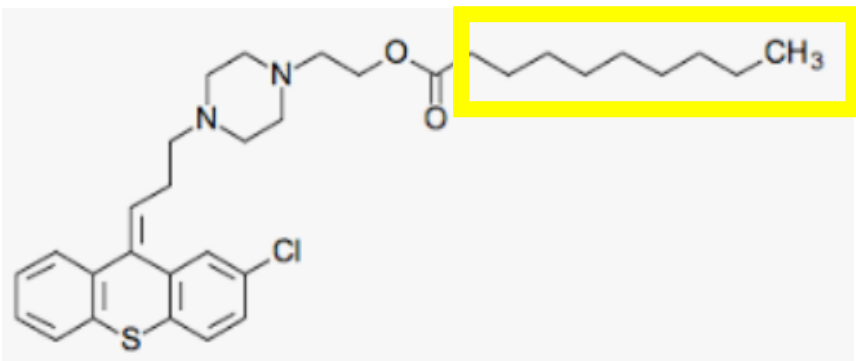


Intervention (IM)	Lorazepam	Clopixol acuphase [®]	Clopixol depot
Onset of action	Tmax: ~15–30 mins Half-life: ~6-8 hours	Tmax: ~36 hours Half-life: ~20 hours	Tmax: ~3-7 days Half-life: ~19 days

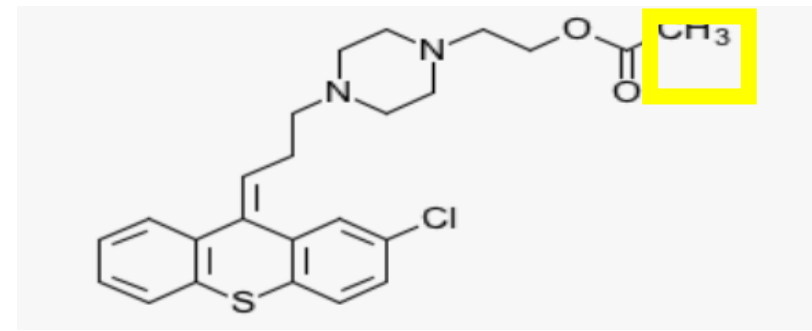
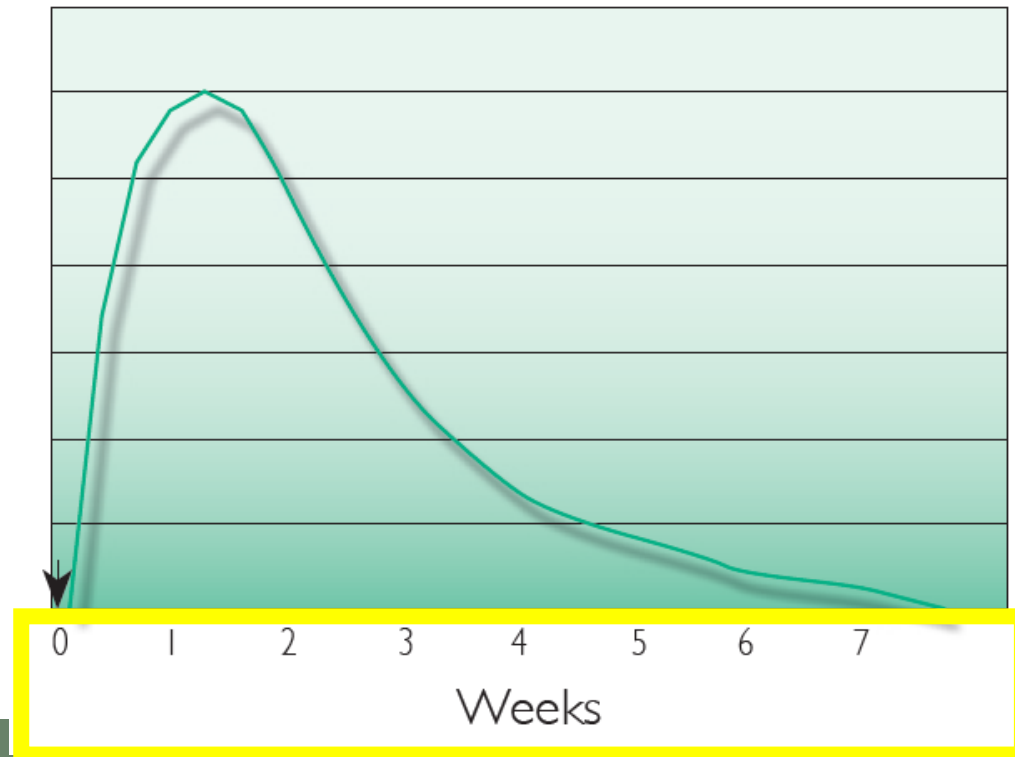
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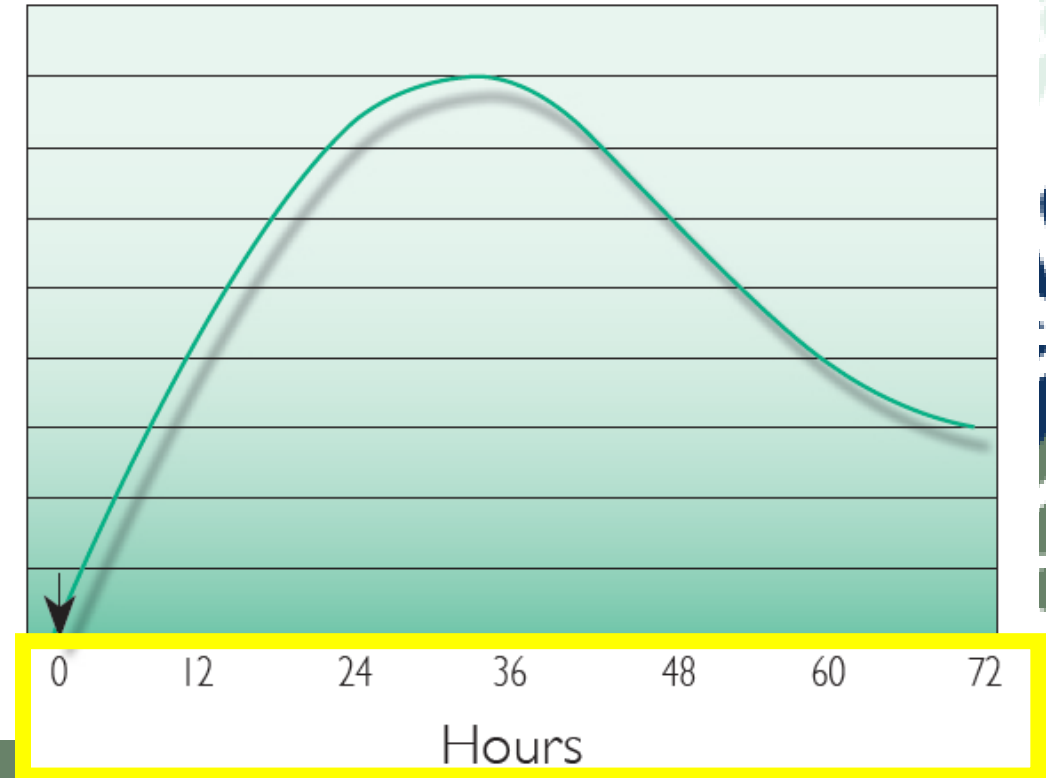
Intervention (IM)	Lorazepam	Clopixol acuphase [®]	Clopixol depot
Onset of action	Rapid	Intermediate	Long-term



Zuclopenthixol decanoate single dose



Zuclopenthixol acetate single dose



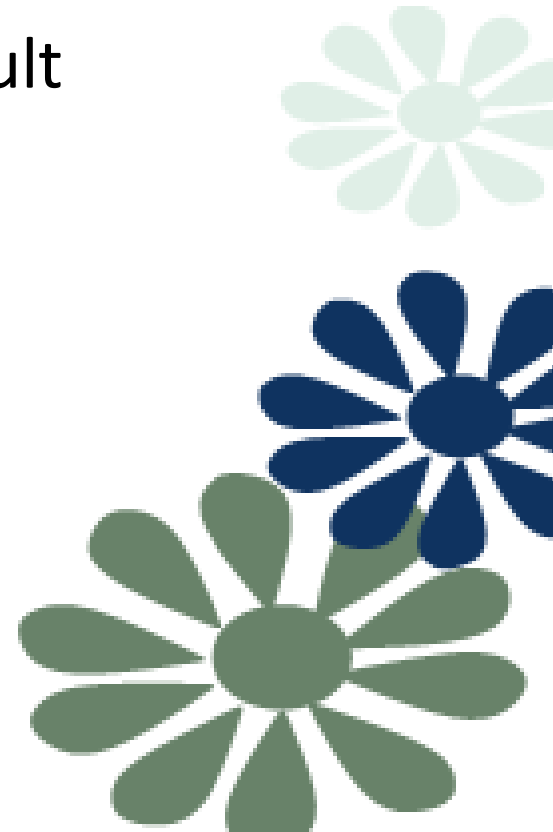
Clopixol acuphase[®]: Cochrane review

- *‘Most of the small trials present important methodological flaws and findings are poorly reported’*
- Not more or less effective in controlling aggressive acute psychosis, or in preventing adverse effects than intramuscular haloperidol
- The use of Clopixol acuphase[®] may result in less numerous coercive injections
- Low doses of the drug may be as effective as higher doses
- Well-conducted pragmatic randomised controlled trials are needed (which is difficult)



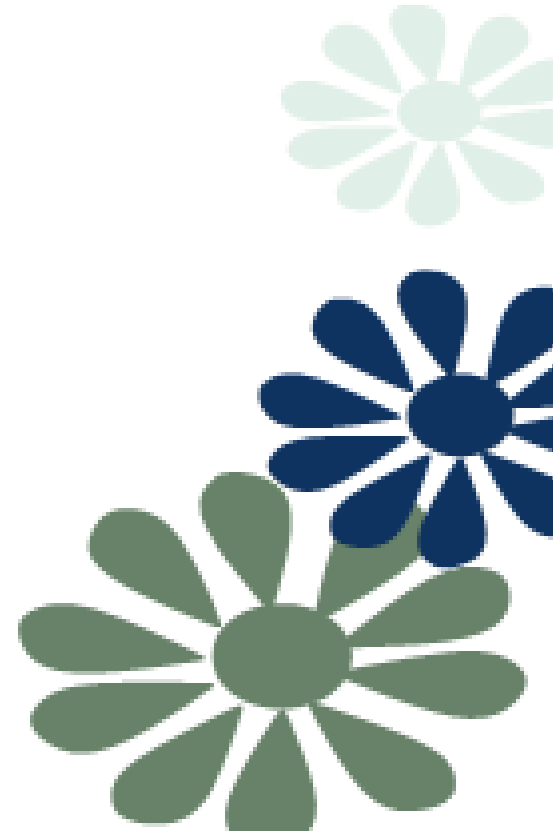
When to use Clopixol acuphase[®] with caution

- At the same time as other injectable antipsychotics or benzodiazepines (may lead to oversedation which is difficult to reverse)
- Where hepatic or renal impairment is present
- Where cardiac disease is present
- A person who is sensitive to extra-pyramidal side effects
- A patient on high dose antipsychotics or where the use of Clopixol acuphase[®] will put them into high doses
- Where there is a history of seizures



When to avoid Clopixol acuphase®

- A person accepting oral medication
- To a person who is struggling excessively to resist injection who cannot be suitably restrained, as there is a risk of intravasation and oil embolus
- A neuroleptic naïve person
- A person with known hypersensitivity to any of the excipients in Clopixol acuphase®
- A person who is unconscious
- A person who is pregnant
- Where there is a depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates)
- For the management of dementia related behavioural disturbances
- As a test dose for zuclopenthixol decanoate



Clopixol acuphase[®]: dosing

- Offer oral first and thorough review prior to each dose
- 50-150 mg (100mg elderly) per dose
- Minimum dose interval 24 hours (usually 2-3 days) - maximum total dose 400mg (and no more than 4 injections) within a 2 week period
- Review and consider holding oral medication (antipsychotics/sedatives) for ~48 hours post administration



...and of course, it is not a course!



Clopixol acuphase[®]: side effects

Common

- Drowsiness
- Movement disorders (akathisia, dystonia, parkinsonian symptoms)
- Raised Prolactin
- Constipation
- Hypotension

Less Common

- Tachycardia
- Urinary retention
- Prolong QT interval
- Neuroleptic malignant syndrome (NMS)



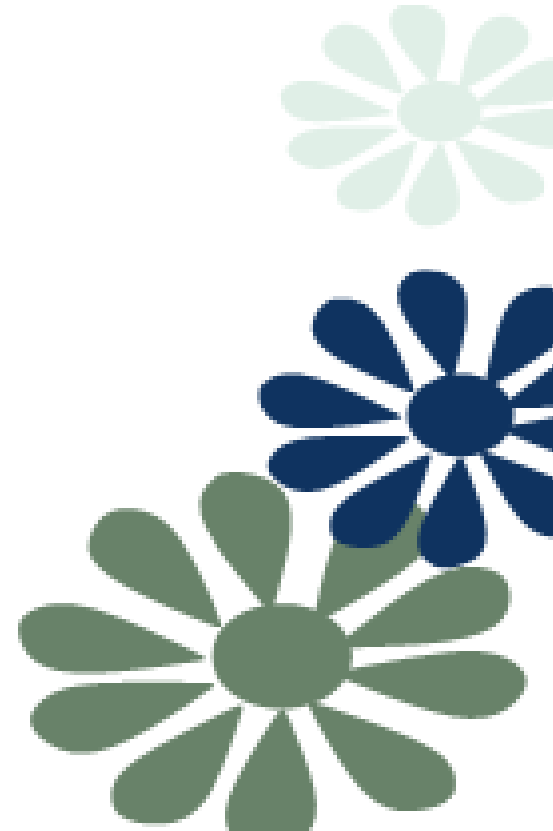
Clopixol acuphase[®]: monitoring

- NEWS2 chart: blood pressure (BP), pulse, temperature, respiration rate, SpO2, consciousness
- Non-contact obs: Alert, Voice, Pain, Unresponsive and EPSEs
- Baseline, 15 mins, 30 mins then at 1, 2, 4, 6, 8, and 12 hours after the injection, then every 6 hours up to 48/72 hours
- ECG once calm and able
- HDM if combined antipsychotic dose over 100% BNF



Clopixol acuphase[®]: post-administration

- Staff debrief
- Patient debrief (advanced decision?)
- Documentation
 - Prescription chart
 - Clinical notes
 - Chemical restraint is a form of restrictive intervention and is required to be incident reported to the national Mental Health Services Data Set





10 x 1 ml ampoules
PL 0458/0017 MA090/00303

Clopixol® Injection

200 mg in 1 ml

Solution for injection
zuclopenthixol decanoate

For maintenance treatment by deep intramuscular injection only

Lundbeck Ltd.
Milton Keynes, MK7 6BZ, UK

POM



5 x 1 ml ampoules
PL 0458/0063

Clopixol-Acuphase®

50 mg in 1 ml

Solution for injection
zuclopenthixol acetate

For initial treatment by deep intramuscular injection only

Lundbeck Ltd.
Milton Keynes, MK7 6BZ, UK

POM



5 x 1 ml ampoules
PL 0458/0060

Clopixol® Conc. Injection

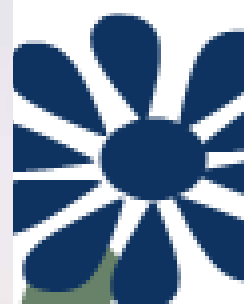
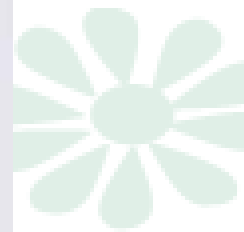
500 mg in 1 ml

Solution for injection
zuclopenthixol decanoate

For maintenance treatment by deep intramuscular injection only

Lundbeck Ltd.
Milton Keynes, MK7 6BZ, UK

POM







Summary

- Prevention is better than the cure
- Review all regular treatment before/during episodes of acute disturbance
- Consider (and pre-empt) treatment delay where at all possible
- Clopixol acuphase[®] is a niche medication to be used in a limited set of situations
- It can be very beneficial (when used appropriately) but requires careful monitoring and review



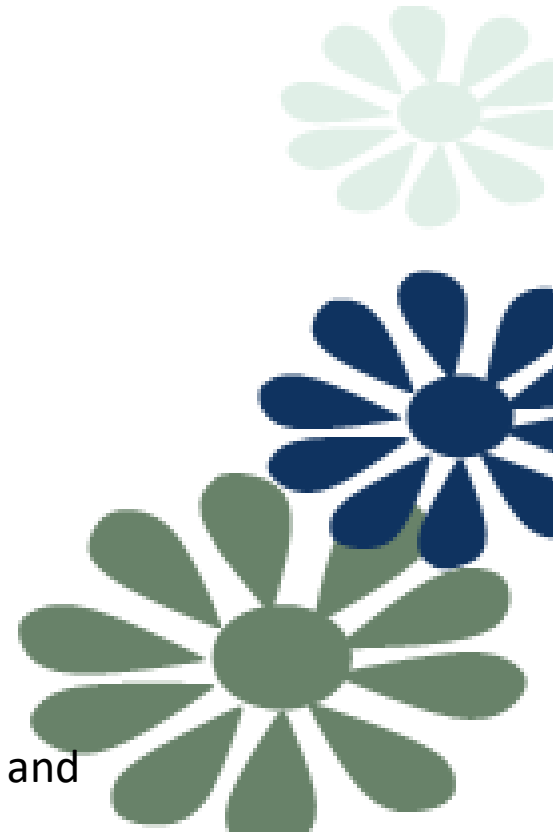
References

- Bazire. S. *Psychotropic Drug Directory 2018 – The Professionals’ Pocket Handbook and Aide Memoire*. 2018. (graphs)
- Bazire. S. *Psychotropic Drug Directory 2020/21 – The Professionals’ Pocket Handbook and Aide Memoire*. 2020.
- Cochrane Database of Systematic Reviews 18.4.2012, Issue 4. Art. No.: CD000525. Jayakody K, Gibson RC, Kumar A, Gunadasa S. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses
- Correll. C. et al. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. *CNS Drugs*. 35(1): 39–59. 2021.
- Drugs and Therapeutics Committee. Devon Partnership NHS Trust. Safe and Appropriate Use of Clopixol Acuphase (Zuclopenthixol acetate). Prescribing Guideline. PG21. 2019.
- El Abdellati. K, De Picker. L, Morrens. M. Antipsychotic Treatment Failure: A Systematic Review on Risk Factors and Interventions for Treatment Adherence in Psychosis. *Frontiers in Neuroscience*. Volume 14. 2020
- Haddad. P. M, Brian. C, Scott. J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Related Outcome Measures*. 5: 43–62. 2014.



References

- Kyoto Encyclopedia of Genes and Genomes. KEGG DRUG Database. 2023. Last accessed 26/01/2023. [<https://www.genome.jp/kegg/drug/>]
- Lieberman. J. A, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The New England Journal of Medicine. 353: 1209-1223. 10.1056/NEJMoa051688. 2005.
- Lundbeck Limited. Clopixol Acuphase Solution for Injection 50mg/ml Summary of Product Characteristics. Last updated 26/1/17 Available at [www.medicines.org.uk] Last accessed 01/02/2023
- Lundbeck Limited. Clopixol 200mg/ml solution for injection. Summary of Product Characteristics. Last updated 10/2022. Available at [www.medicines.org.uk] Last accessed 01/02/2023
- Lundbeck Limited. Clopixol Conc. 500mg/ml solution for injection. Summary of Product Characteristics. Last updated 10/2022. Available at [www.medicines.org.uk] Last accessed 01/02/2023
- Mancuso. C. E, Tanzi. M. G, Gabay. M. Paradoxical reactions to benzodiazepines: literature review and treatment options. Pharmacotherapy. 24(9):1177-85. 2004.
- Morken. G, Widen. J. H, Grawe. R. W. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry. 8: 32. 2008.



References

- National Institute for Health and Care Excellence. *Violence and aggression:short-term management in mental health, health and community settings [NG10]*. London: NICE; 2015.
- Patel et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. *Journal of Psychopharmacology* 2018;1-40
- Taylor. D, Barnes. T, Young. A. *The Maudsley Prescribing Guidelines in Psychiatry*. 14th Ed. 2021.

