

# Multidisciplinary Management of Acute Disturbance

## Depot Pharmacokinetics & Loading – is it relevant?

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*(No Declarations of Interest)*

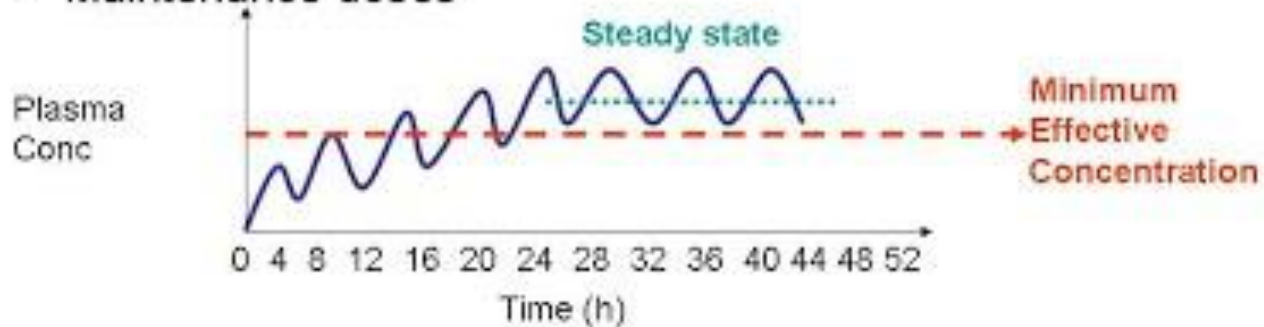
# Steady state

- Reach target steady-state levels for maximum safety and efficacy.
- Steady-state is a function of the elimination half-life of the drug.
- Approximately 5-7 half-lives of the drug.
- Using loading doses to achieve therapeutic levels on the first dose.

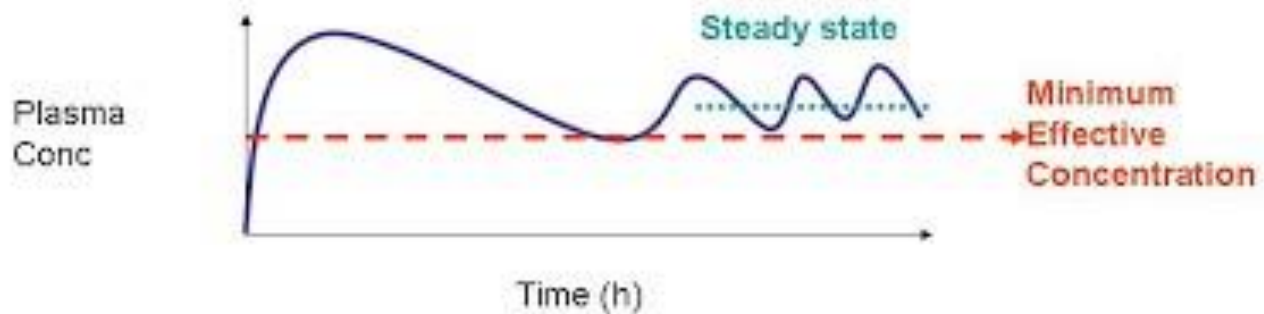
# of half-lives	% of Steady-State
1	50%
2	75%
3	87.5%
4	93.8%
5	96.9%

# Loading doses

- Maintenance doses



- Loading dose and Maintenance doses



# Depot antipsychotic pharmacokinetics

Active Ingredient	Doses Starting mg Maintenance mg	Peak levels	Half life	Steady state
Flupentixol decanoate Depixol®	<b>20</b> <i>50–300 every 2–4 weeks</i>	7 days	8-17 days	~ 9 weeks
Fluphenazine decanoate Modecate®	<b>12.5</b> <i>12.5 – 50 every 2–3 weeks</i>	8-12 days <i>(6-48 hours)</i>	10 days	~ 8 weeks
Haloperidol decanoate Haldol®	<b>50</b> <i>50–200 every 3–4 weeks</i>	7 days	21 days	~ 14 weeks
Zuclopenthixol Decanoate Clopixol®	<b>100</b> <i>200–500 every 1–4 weeks</i>	4-7 days	19 days	~12 weeks

# Equivalent doses

Antipsychotic injection	Dose	Interval	Maximum Dose/wk (% CPZ 1000mg)
Flupentixol decanoate	20mg	2 weeks	400mg (400%)
Fluphenazine decanoate	10mg	2 weeks	50mg (100%)
Haloperidol decanoate	30mg	2 weeks	75mg (50%)
Zuclopenthixol decanoate	200mg	2 weeks	600mg (60%)

# Rapid Response Report

NPSA/2010/RRR018

From reporting to learning

25 November 2010

## Preventing fatalities from medication loading doses

- Produce a list of critical medications
- Effective communication regarding loading dose and subsequent maintenance dose regimens when prescribing, dispensing or administering critical medicines.
- Clinical checks are performed by medical, nursing and pharmacy staff to ensure that loading and maintenance doses are correct.
- Healthcare professionals in the community know when to challenge abnormal doses of the identified critical medicines.



# **The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal**

*Ther Adv Psychopharmacol*

2014, Vol. 4(5) 198–219

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Sofia Brissos, Miguel Ruiz Veguilla, David Taylor and Vicent Balanzá-Martinez

## **Many advantages**

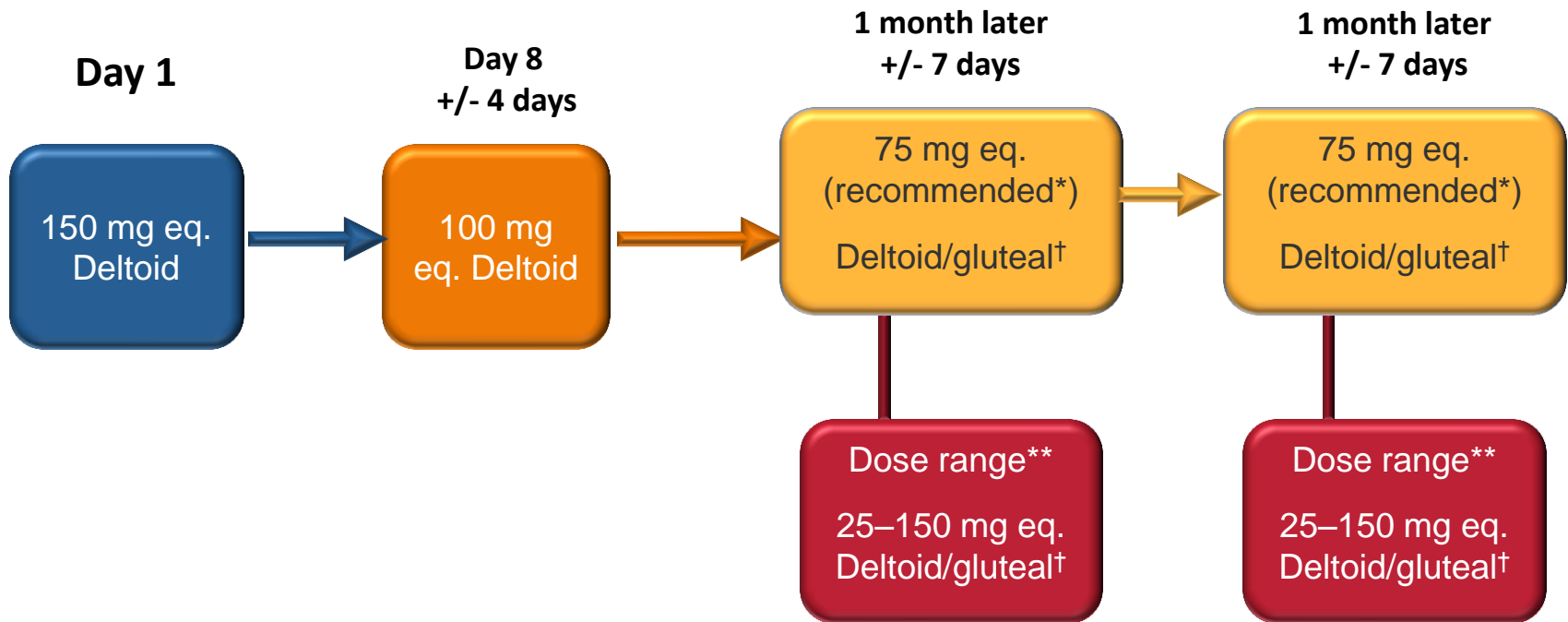
## **The disadvantages included**

- Slow dose titration
- Longer time to achieve steady state levels
- Less flexibility of dose adjustment
- Delayed disappearance of distressing and/or severe side effects

# Paliperidone loading dose

## INITIATION REGIME

## MAINTENANCE REGIMEN (1 month after 2nd initiation dose)



\*Recommended monthly dose

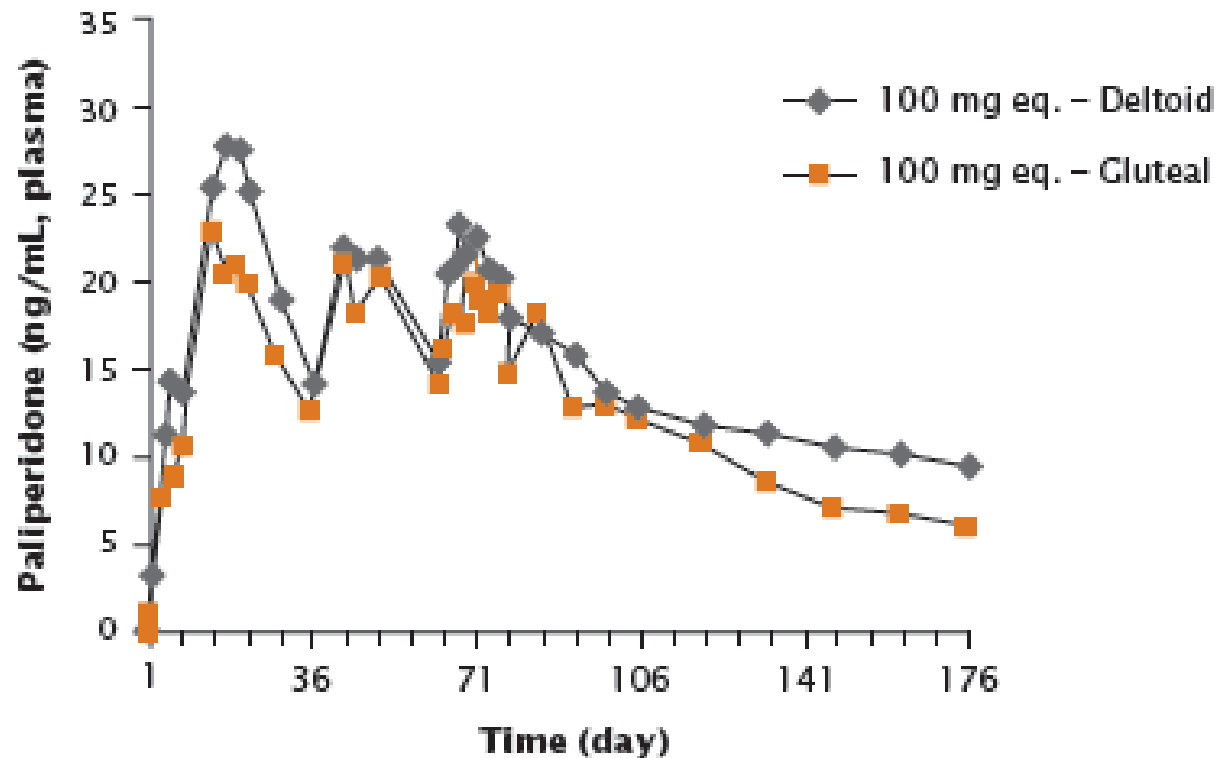
\*\*Some patients may benefit from lower or higher doses based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range

†A switch from gluteal to deltoid (and vice versa) should be considered in the event of injection site pain (if discomfort is not well tolerated). It is also recommended to alternate between left and right sides



# Paliperidone

Figure 2. Median paliperidone plasma concentration–time profiles



# Aripiprazole Maintena<sup>®</sup>

- Establish tolerability with oral aripiprazole prior to initiating treatment.
- Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability.
- After the first injection treatment with oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic should be continued for 14 consecutive days.

# Use of oral to supplement/establish efficacy of depots

- Steady state for oral is more rapid
  - Flupentixol  $T_{1/2} = 35$  hrs SS = 8 days
  - Haloperidol  $T_{1/2} = 24$  hrs SS = 5.5 days
  - Zuclopenthixol  $T_{1/2} = 24$  hrs SS = 5.5 days
- Can 'tailor' to reduce burden of side effects
- Ensure oral is reduce as depot established to avoid HDAT

# Equivalent doses

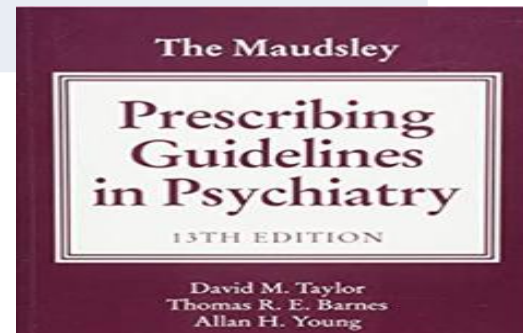
Antipsychotic injection	Dose	Interval	Oral equivalent
Flupentixol decanoate	20mg	2 weeks	3 mg a day
Fluphenazine decanoate	10mg	2 weeks	2mg a day (Not available in UK)
Haloperidol decanoate	30mg	2 weeks	2 mg a day
Zuclopenthixol decanoate	200mg	2 weeks	25mg a day

# Clozapine

- Doses titrated up slowly due to effects on BP and HR and to prevent side effects such as seizures, sedation, hypersalivation and constipation.
- Clozapine is gradually titrated over the first 14 days and the patient is monitored carefully during the titration.
- Previously been on clozapine and tolerated a normal titration a quicker titration can be used. This should only be used where the person is fit and well with no other co-morbid conditions.

# Clozapine

Time since last dose	Action to re-start
Up to 48 hrs	Re-start at previous dose – no titration
48-72 hrs	<b>Begin rapid re-titration as soon as possible</b> Day 1 – 50% dose (divided 12 hrs apart) Day 2 - 75% Day 3 – 100% (if tolerated)
72 hrs to 1 week	<b>Begin re-titration with 12.5mg or 25mg</b> Try 2 <sup>nd</sup> dose at 12 hrs later if well tolerated. Increase to ‘normal’ dose according to tolerability over at least 3 days
More than 1 week	<b>Re-titrate as if a new patient</b> Aim to reach dose within 2-4 weeks



# Lithium

- The low therapeutic index
- Low dose and increased incrementally every 5–7 days depending on results of serum lithium levels.
- Thus, not a therapeutic dose for first week.
- Previous levels and response
- Caution with dehydration
- Watch for side effects – coarse tremor, D&V
- Non adherence

# Valproate

## Depakote<sup>®</sup>

- 750 mg on day 1 and 20 mg/kg+ on day 2.
- >45 mg/kg/day should be carefully monitored.

## Epilim<sup>®</sup> (not licenced)

- 20 – 30 mg/kg/day body weight.
- Increased to 2500 mg per day.

Avoid in women of childbearing potential



# Carbamazepine

- Initially 400 mg daily in divided doses
- Usual dose 400–600 mg daily
- Maximum 1.6 g per day
- Auto-inducer therefore increase in steps of 100–200 mg every 2 weeks
- Test for HLA-B\*1502 allele in individuals of Han Chinese or Thai origin
- Cytochrome P450 inducer therefore interacts with many antipsychotics

# Summary

- Loading dose of depots **not recommended.**
- Loading doses of long acting injections as per SmPC is recommended.
- Ensure prescribing plans clear and concise and documented.
- Involve MDT
- Reduce oral as depot established
- Optimise doses but monitor for adverse effects

# Thank You

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