



# Patient Adherence In A Medication Regimen of BID vs TID: A Randomized Simulation Trial

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## BACKGROUND

Previous studies have reported no significant differences in efficacy between BID (twice a day) vs TID (three times a day) regimens of the same daily dose of medication for both antibiotic and chemotherapy agents<sup>1,2</sup>. The studies investigated factors such as medication side effects, safety, response rates, pharmacokinetics and pharmacodynamics. It is believed physicians prefer to prescribe a pill regimen with a lower frequency based on the assumption that patient adherence improves with fewer doses. This is mostly based on patient preference and self-evaluation to the physician. However, patient adherence has not been fully investigated.

Previous studies have reported no significant differences in efficacy between BID vs TID dosing. Missing one dose of a BID schedule is 50% of the daily dose, while missing a TID dose is 33% of the daily dose. The purpose of this study is to simulate BID and TID dosing of a 10-day pill regimen to investigate adherence differences and its implications in therapeutic consequences.

## METHODS



- Healthy volunteers ≥18 years old who did not have specific training in healthcare were randomized to a twice daily (BID) or three times daily (TID) regimen of candy pills to treat a simulated pneumonia.
- Volunteers sent an email or text message to one of the study researchers for each dose “taken” confirming the dose and its time.
- At the end of the study remaining pills were counted and reported back to study researchers.
- 1 subject was excluded due to >70% pills missed.

### Outcome Measure Definitions

	Early Doses	Late Doses	Extra Doses
BID	<7.5 hours	>16.5 hours	≥ 3 doses/day
TID	<5 hours	>11 hours	≥ 4 doses/day

## RESULTS

Table 1. Participant Demographics

	BID (n=24)	TID (n=18)	p-value
Sex (M/F)	11/13	6/12	0.41
Age	29.9 ± 1.9	31.0 ± 3.0	0.32

### Participant Demographics

- There was no group difference in sex distribution
- Participants in both groups were similar in age
- Study participants were highly educated (most had a college degree)

Fig 1. Percent Of Participants In The BID vs. TID Group Who Missed At Least 10% And 20% Of The Total Dose Over the 10-Day Regimen

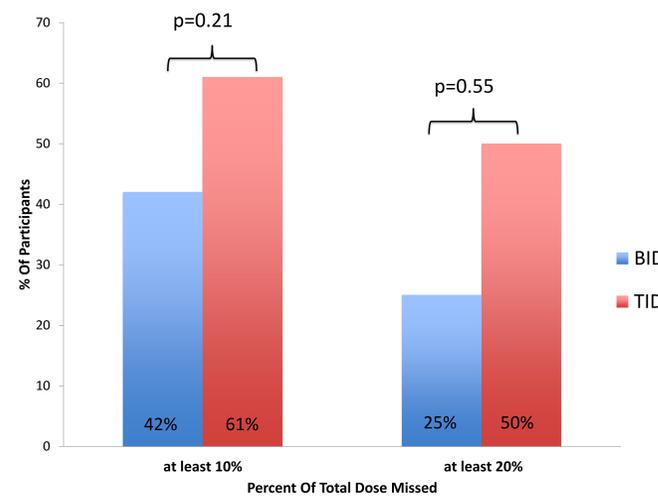


Fig 1: Though more TID participants missed at least 10% and at least 20% of the total regimen dose than BID participants, there were no significant group differences.

Fig 2. Average Number Of Missing, Early, Late, and Extra Doses By Group

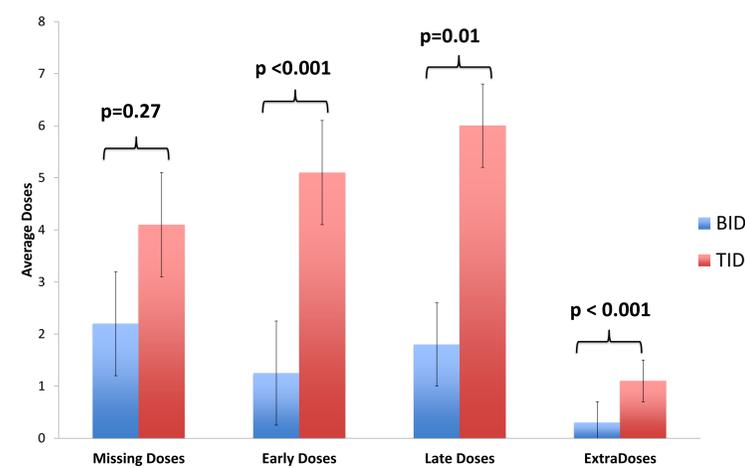


Fig 2: TID participants had significantly more early doses (p<0.001), late doses (p=0.01), and extra doses (p<0.001) than BID participants over the 10-day regimen.

Fig 3. Differences In The Correct Daily Dose Adherence By Treatment Day

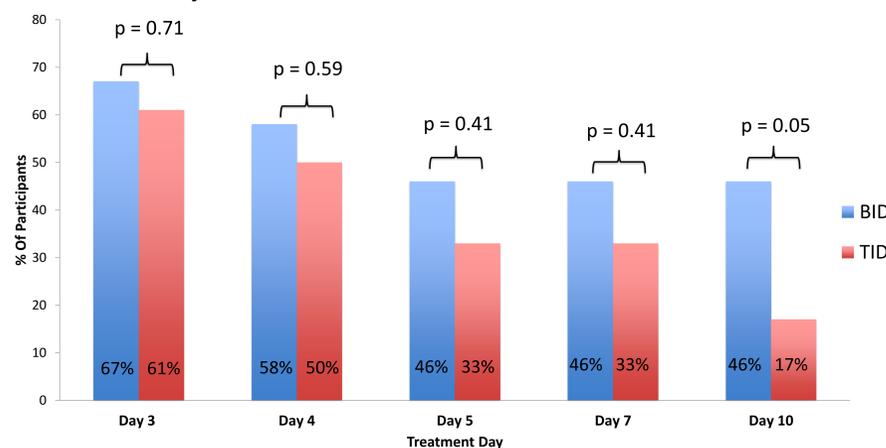


Fig 3: By treatment day 10, however, BID participants tended to more likely take the correct daily dose compared to TID participants, (46% vs. 17%, p = 0.05).

- There was no significant difference in the percent of participants who took the correct daily dose on day 3, 4, 5, and 7.
- There was no group differences in the total mg dose between the groups on treatment days 3, 4, 5, 7, and 10. (data not shown)

## CONCLUSIONS

- BID dosing had significantly fewer mis-timed and extra doses per day than TID dosing
- There was no significant difference in the total dose taken throughout the 10-day course. However, there was a trend for better adherence to a BID course at day 10. This study suggests that in longer antibiotic courses (> 7 days), a BID regimen may lead to better adherence
- Timely adherence to an antibiotic regimen appears to be more challenging with a higher number of daily doses. Results of this study suggest that frequency of daily dose is directly associated with mis-timed doses.

## DISCUSSION

### Clinical application:

- This study shows a TID regimen has statistically more early, late and extra doses of the regimen indicating medications with narrow therapeutic windows will benefit from a BID or once daily medication regimen
- Amoxicillin-clavulanate at a dose of 875 mg 60% is excreted in urine within 6-8 hours, with a peak blood concentration 1.5 hours after administration. No recommendations of doses >875 mg/dose can be made due to C<sub>max</sub> not achieving a plateau in previous studies<sup>1</sup>

### Patient adherence:

- A 2014 Cochrane review did not identify a specific intervention that statistically improved patient adherence
- Patient's tended to miss doses when they were out of the house (at work, school, etc.). Targeting an intervention for these doses could prove beneficial

### Study Limitations:

- Simulation study: no illness may blunt adherence since no health implications and the influence of medication side effects on adherence could not be investigated.
- Study done on subjects ≥18 years old, previous data indicate children have better adherence due to parent administration and motivation.
- Study participants were highly educated therefore not reflective of the general population.
- Hawthorne effect: subjects had to report medication administration to researchers.

## REFERENCES

1. Falagas ME, et al. "Compliance with Once-Daily versus Twice or Thrice-Daily Administration of Antibiotic Regimens: A Meta-Analysis of Randomized Controlled Trials." *PLOS ONE*, Jan. 2015.
2. Nieuwlaat R, et al. "Interventions for enhancing medication adherence (Review)." *Cochrane Database of Systematic Reviews*, 2014.

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