

## Refill non-adherence to repeat prescriptions leads to treatment gaps or to high extra costs

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**Abstract Objective:** To determine the nature and extent of undersupply and the economic consequences of oversupply of medication among non-adherent patients. **Methods:** This study used copies of repeat prescriptions (= multiple dispensations), collected during 1 week in 2002 at 16 Swedish community pharmacies. For patients with a refill adherence below 80%, treatment gaps were defined as the number of days they had no drug available. The cost of drug oversupply (i.e., refill adherence >120%) was calculated from the prices of the drug packages dispensed. **Results:** The number of collected repeat prescriptions was 3,636. The median of treatment gaps among patients with a refill adherence below 80% was 53 days per 90–100 days treatment period and the corresponding median for oversupply was 40 days. The cost of oversupply for exempt patients (i.e., patients who have paid 1,800 SEK (€ 196; US\$ 243) per year for medicines) was 32,000 SEK (€ 3,500; US\$ 4,300) higher than for non-exempt patients. An extrapolation to all Sweden indicates that exemption from charges leads to an additional oversupply of about 142 million SEK (€ 15 million; US\$ 19 million) per year above that of non-exempt patients. **Conclusion:** Both undersupply and oversupply of prescribed medicines are common in Sweden. Patients with a refill adherence below 80% seem to have less than half of the prescribed treatment available. Oversupply or drug

stockpiling occurs more frequently among exempt than among non-exempt patients, and this oversupply leads to high unnecessary costs.

**Key words** Costs · Exemption from charges · Oversupply · Refill adherence · Repeat prescriptions · Treatment gaps · Undersupply

### Introduction

Optimal drug treatment necessitates adequate adherence to the given prescription. The non-adherence involved has attracted many researchers and there is a vast literature on patient adherence or non-adherence to prescribed medication. In October 2004, the MEDLINE database gave 1,801 references to the search words *adherence and drugs* and 7,409 references to *compliance and drugs*. The literature on adherence has recently been reviewed by WHO (World Health Organization) [1]. They indicate that research on patient adherence has mostly been concerned with the level of adherence in different settings or diseases and/or with interventions to improve adherence [1]. Non-adherence may involve both undersupply and oversupply in addition to other inappropriate medication behaviour. Most studies deal with drug undersupply, often with the focus on the factors explaining adherence or non-adherence [1].

In a recent study [2] we used repeat prescriptions to estimate refill adherence among Swedish patients. Satisfactory refill adherence was defined as dispensed refills covering 80–120% of the prescribed treatment time. The estimation of refill adherence from prescription records has been claimed to be the most reliable objective measure of adherence in large patient groups [3, 4]. Therefore, refill adherence data have been used by several authors as a proxy for patients' total therapeutic adherence [3–6].

There are few studies in which the consequences of undersupply or oversupply have been studied. In one

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study on undersupply among patients with antipsychotic medication [7], refill adherence data indicated that treatment gaps were common. During 1 year, 51% of the patients had treatment gaps of 30 days or longer. In other studies involving patients with a depression-related diagnosis and cardiovascular diseases, approximately 50% of patients had treatment gaps in their medication [8, 9]. The association between non-adherence and morbidity has been described in a Cochrane review [10] which concluded that non-adherence is strongly associated with increased morbidity.

The consequences of drug oversupply in long-term medication have been even less studied. Continuous overuse of acetaminophen (paracetamol) seems to be associated with liver failure [11], and overuse of a number of medicines, e.g., ergotamine, may lead to chronic headache [12].

The level of oversupply of medicines may be related to the drug reimbursement level, which varies between the EU countries. In the UK, 85% of the prescription items—provided to over half the population—were exempt from charges on the grounds of age, income or clinical condition [13]. In Sweden, 13% of the population were exempt from charges [14]. All Swedish patients who have paid 1,800 SEK (€ 196; US\$ 243) per year for medication are exempt from charges. The willingness to pay for prescribed medication was found to increase with symptom severity and perceived necessity or effectiveness of treatment [15]. For non-exempt patients, increased charges led to reductions in prescription drug utilisation [16, 17]. The young, the unemployed, and those with poor health status, low education and low income are most likely to decrease consumption of prescription drugs when user charges increase [17]. In these publications [15–17] the levels and consequences of oversupply by patients exempt from charges have not been analysed.

### Aims of the study

The aims of this study were to analyse:

1. To what extent patients who had a refill adherence below 80% of prescribed treatment had gaps in their medication.
2. The relations between exemption from charges and the economic consequences of drug oversupply (above 120% of prescribed treatment).

### Methods

The analysis was based on data from repeat prescriptions collected from 16 Swedish pharmacies [2]. The Swedish pharmacy system has been described elsewhere [18]. Prescriptions are valid 1 year from the date of

issue [19]. A prescription may be dispensed only once or the same prescription form may be used for multiple dispensations (= repeat prescription) as determined by the prescriber. All patients pay the full cost of drugs up to 900 SEK (€ 98; US\$ 122) during a 12-month period, the cost for the patient is then gradually reduced and the patient is exempt from further charges beyond 1,800 SEK (€ 196; US\$ 243) per year.

Each time a repeat prescription is filled at the pharmacy, the date and the amount of drugs dispensed are noted on the prescription form. The repeat prescriptions included here were those that had been dispensed at least twice. Repeat prescriptions are commonly issued for 1 year of treatment, with three-month dispensation intervals. The Swedish drug reimbursement system allows medicines to be purchased to cover a maximum 3 months. A new purchase may be made when 2 of the 3 months have passed (i.e., “early purchase”). This second purchase is also reimbursed. By repeated “early purchases” of medicines, stockpiling with reimbursement is possible.

Each prescription in the study represents a separate individual and a prescription form with multiple dispensations can be seen as a record of the patient’s adherence behaviour, in relation to each prescribed medicine, up to a year before the latest dispensation.

In summary, the inclusion criteria for a prescription to be included were: repeat prescription, dispensed at least twice and with fixed dosing.

The study was based on copies of repeat prescriptions, which were collected during 1 week in November 2002 in the southern Swedish county of Jönköping (population = 328,000). The prescriptions covered all types of prescribed drugs. Copies of prescriptions were collected during 1 week and the adherence on previous fillings was determined retrospectively from the prescription form.

Satisfactory refill adherence was defined as the percentage of the patients who had refills dispensed covering 80–120% of the prescribed treatment time [2, 20] and under- and oversupply as < 80% and > 120% coverage, respectively.

Satisfactory refill adherence

$$= \frac{\text{number of prescribed treatment days}}{\text{number of days between the fills}} * 100$$

$$= 80 - 120\%$$

Ideally, a patient would buy a drug for 100 days treatment with an interval between two refills of 100 days (refill adherence = 100%). A divergence from prescribed treatment time below –20% indicates treatment gaps or undersupply and above +20% means stockpiling or oversupply.

The lengths of the treatment gaps were determined as the number of days that the patients with a refill

adherence below 80% had no drug available for their treatment. More details regarding the methods used have been presented elsewhere [2].

The cost of oversupply was determined separately for exempt and non-exempt patients, both groups with a refill adherence above 120%. The price of each drug package dispensed was obtained from the official drug price list of November 2002. There is no VAT for prescribed medication in Sweden and the prices of the official list include the pharmacist's fee. From the price and the prescribed dosage, the cost of medicines per day could be calculated. To determine the cost of oversupply, the number of days beyond 120% coverage for each prescription was multiplied by the cost per day. Thus, the total cost of drug oversupply (refill adherence above 120%), as well as the separate costs attributed to non-exempt and exempt patients were calculated. An extrapolation of the approximate cost of oversupply for repeat prescriptions in all Sweden during 1 year was based on the assumption that a representative sample of prescriptions had been studied, as discussed below.

Median and interquartile deviations were calculated for under- and oversupply and were limited to repeat prescriptions with 90–100 days dispensation intervals (1,152 prescriptions). The remaining 426 prescriptions showed a wide variety of dispensation intervals which make the median deviation difficult to interpret. Statistical significance was determined using *t*-test.

## Results

The number of collected copies of repeat prescriptions, with notifications that there had been at least two dispensations, was 3,636 or 33% of the total number of dispensed repeat prescriptions at the participating pharmacies [2]. The average level of satisfactory refill adherence was 57%. Patients with full exemption from charges had lower satisfactory refill adherence (51%) than those without exemption (58%). This was mostly due to oversupply. The level of under- and oversupplies was 21% and 22%, respectively (Table 1) [2]. There was a larger oversupply (33%) among patients with full exemption compared to those without exemption (19%). Non-exempt patients had 22% undersupply as compared to 16% for exempt patients (Table 1).

The total number of prescription forms with a refill adherence below 80% was 762, i.e., 21% of the total number of prescriptions. The prescribed dispensation intervals were normally 90–100 days and the median of the treatment gaps per interval was  $53 \pm 23$  (interquartile deviation) days, i.e., more than half of the prescribed treatment time.

The number of prescription forms with a refill adherence above 120% was 816 and among those, 299

patients were exempt from charges. The median number of days with oversupply or drug stockpiling per 90–100 days dispensation interval was  $28 \pm 6$  (interquartile deviation) days per interval. The total sales value of the 3,636 repeat prescription forms was 5.1 million SEK (€ 0.55 million; US\$ 0.69 million). The extra cost of oversupply for all the patients in our study was 230,000 SEK (€ 25,000; US\$ 31,000) or about 4.5% of the total sales value of all dispensations of repeat prescriptions in the study. The extra cost resulting from oversupply among the 517 non-exempt patients was 99,000 SEK (€ 11,000; US\$ 13,000) or 191 SEK per prescription form (€ 21 or US\$ 26) and among 299 exempt patients 131,000 SEK (€ 14,000; US\$ 18,000) or 438 SEK per prescription form (€ 48; US\$ 59) ( $P < 0.05$ ). Therefore, the difference in cost of oversupply between exempt and non-exempt patients amounts to 32,000 SEK (€ 3,500; US\$ 4,300). The average number of dispensations per prescription form was 3.

The cost of oversupply from our sample can be used for extrapolation. The extra cost for exempt compared to non-exempt patients with oversupply for 1 year in Sweden amounts to 142 million SEK (€ 15 million; US\$ 19 million). This is about 0.6% of the cost of all prescribed medicines in Sweden in 2002 (total cost 24,067 million SEK; € 2,616 million; US\$ 3,252 million) [21].

## Discussion

There are several methods available to estimate adherence to prescribed medication [22]. This may include the measurement of the drug levels in plasma or urine or electronic monitoring (medication event monitoring system (MEMS)) which records the time and date when a medication container was opened. These are expensive methods [1]. Other procedures like asking the patients to estimate their own adherence or counting remaining dosage units are less reliable. However, these measurements easily overestimate the adherence [1]. Although, data from prescription records are useful in determining refill adherence in large patient groups [3, 4], it's important to be aware of the limitations. Medication supply may diverge from medication use and under- and oversupply from under- and overuse and fluctuate over time for an individual patient. The patients may also have more than one prescription for the same drug. In such a case an adherent patient would be classified as non-adherent with undersupply. Doctors may also orally adjust the doses up or down. That patient would deviate from what the doctor has prescribed but still be adherent to the doctors' oral advice.

**Table 1** Refill adherence in relation to patient reimbursement

	Number of prescription forms	Prescription forms with satisfactory refill adherence <sup>a</sup> (%)	Prescription forms with undersupply <sup>b</sup> (%)	Prescription forms with oversupply <sup>c</sup> (%)
Exempt from charges	906	51	16	33
Non-exempt from charges	2,730	58	22	19
All patients	3,636	57	21	22

<sup>a</sup>80–120%<sup>b</sup>Refill adherence < 80%<sup>c</sup>Refill adherence > 120%

Apoteket AB (The National Corporation of Swedish Pharmacies) estimates that 40% of prescriptions dispensed at Swedish pharmacies are repeat prescriptions (at least one refill). This would correspond to 11,200 such prescriptions at the participating pharmacies during the study period. We were informed that due to lack of time at some pharmacies they did not copy all repeat prescriptions. As a result we got copies of 3,636 prescriptions (33%), which can be seen as a limitation. Another limitation in our study is that some of the prescriptions may be intended for temporary medication only. However, such information was not apparent from the prescription forms. All prescriptions dispensed at least twice were therefore included, although this may lead to an overestimation of the extent of treatment gaps.

In our study the levels of under- and oversupply among patients with repeat prescriptions were similar, 21% and 22%, respectively. In many previous studies satisfactory medication adherence has arbitrarily been set at  $\geq 80\%$  [23]. Levels below 80% may signify treatment gaps, i.e., periods when the patients theoretically do not have medicine available and therefore have no possibility to be adherent.

Most studies do not indicate an upper level of satisfactory adherence, probably because data on oversupply are more difficult to interpret than those of undersupply. There are, however, reports [20] in which  $100 \pm 20\%$  as been used to indicate of “good compliance.” Since also very frequent refills of the drug supply might indicate a deviation from the prescribed treatment, oversupply was included in this study. It is possible that oversupply signifies intake of too much of the prescribed medicines, but the patients may also be stockpiling medicines, particularly if they are exempt from payment.

Most previous studies using repeat prescriptions to determine refill adherence have obtained their information from encrypted population-based data sources [3]. The refill behaviour of each registered individual can then be ascertained. Swedish integrity legislation has so far with some exceptions hindered establishment of such registers. Therefore, we obtained the information used here from copies of repeat prescriptions and the patient identities remained confidential

with us. However, we assume that each prescription in our sample represents a separate individual, since the copies were all collected during 1 week and it is unlikely that a person would have two prescriptions filled with the same drug during the same week.

Patients who have a refill adherence of 80% are at the lower limit of satisfactory refill adherence as defined here. At 80% refill adherence they could be lacking drugs for 18 of the normal 90 days treatment period unless they have medicines left over from a previous period. A treatment gap of 18 consecutive days could possibly lead to a therapeutic failure depending on the type of disease and treatment. This is especially the case for patients with an HIV infection [24]. We found that 21% of the patients ( $n = 762$ ) had a refill adherence below 80%. The median of treatment gaps for these patients were 53 days of the normal 90–100 days of dispensation interval. These patients would then be without medication more than half of their treatment time. The long dispensation intervals used in Sweden (normally 3 months) may thus impair treatment since non-adherence may go undetected for an unnecessarily long time. A Cochrane review showed that the relation between morbidity and non-adherence in most studies has not been well documented. In cases where this has been done, the data indicate that non-adherence is strongly associated with increased morbidity [10]. Patients with a refill adherence below 80% may therefore be at serious risk of unnecessary morbidity. Since the identities of the patients were confidential in this study, there was no possibility to further explore the health aspects. However, since non-adherence is associated with increased morbidity, prescribers and pharmacists should observe this problem and create concordance with their patients. If concordance is reached at every patient encounter, adherence will be achieved [1].

The number of patients with oversupply (22%;  $n = 816$ ) was similar to the number with undersupply (21%;  $n = 762$ ). Among those with oversupply there were almost twice as many with full exemption compared to those who paid for their medicines (33 vs. 19%). Drug oversupply may indicate drug over-consumption and drug dependence and might lead to medical problems. In this study analysis was limited to

the economic consequences of drug oversupply since available data did not allow analysis of the medical consequences.

We were able to determine the extra cost of oversupply among exempt patients in our sample to 32,000 SEK (€ 3,500; US\$ 4,300). Extrapolation of this cost to the whole of Sweden may be justified knowing that the level of drug prescription in relation to the population of the county of Jönköping is approximately equal to that of Sweden (37 and 38 DDD per inhabitant, respectively, in November 2002) [25]. The number of prescriptions dispensed during the month of November is close to 1/12 of the number for the whole year. Accordingly, we consider the sample to be representative of repeat prescribing in Sweden in 2002. We found that among patients with oversupply, those who were exempt from charges had 142 million SEK higher drug cost than the patients who were non-exempt. This represents 0.6% of the cost of prescribed medicines in Sweden in 2002.

It is unlikely that the frequent refills that the exempt patients with oversupply make are therapeutically motivated. Rather, these patients may be stockpiling medicines, knowing that they can obtain the medicines without a charge. Pharmacists have reported that exempt patients ask their doctors to prescribe additional medicines, even drugs available without a prescription. The oversupplies among non-exempt patients also indicate stockpiling. Therefore, the extrapolated Swedish cost of 142 million SEK per year for oversupply of medicines, may be an underestimation of the actual costs.

There are few reports in the literature on the reasons for oversupply of medicines [15–17], but economy is likely to be of importance. It may be speculated that the differences between non-exempt and exempt patients reflect an underlying need for the former to budget and plan to pay for medicines to be purchased and the latter not needing to budget at all. A limitation of our study is that we have not analysed differences in the mix of medicines that were used by the two groups. To make such an analysis meaningful we would have needed information on all medicines used by each individual and probably also about disease states. Such information was not available. Both groups, however, had similar age and gender distribution.

Much of the drugs stored in patients' homes will never be used because of oversupply, changed medication, side effects, low patient compliance or the patient may die [26]. Many packages are therefore returned to the pharmacies for destruction. The amount of drugs returned to Swedish pharmacies has been estimated to about 4.6% of concomitant sales in volume with a value of 600 million SEK (€ 65 million; US\$ 81 million) per year [27]. This indicates that drug stockpiling may be considerably larger than what we

have estimated from the refill adherence of repeat prescriptions.

Our study has implications for both patients and professionals. Patients should be aware of the importance of the gaps in their medication if they fail to fill their repeat prescriptions. On the other hand they should know that the cost of oversupply is considerable and unjustified. Professionals should also observe both these factors. They should advise the patients to fill their prescriptions as intended and to avoid oversupply.

The results presented in this report might stimulate future research on how refill adherence is dependent on e.g., the reimbursement system. Our study does not reveal the clinical outcomes either of undersupply or oversupply. Such investigations in relation to long-term treatments would be important. The relatively long periods used in Sweden between refills may leave non-adherence undetected and it could also stimulate oversupply. A comparison between three-month and one-month dispensation intervals would therefore be of interest.

## Conclusion

Both undersupply and oversupply of prescribed medicines are common. Patients with a refill adherence below 80% have medicines available for less than half of the proper treatment. Patients with an oversupply above 120% may overuse their medicines, but their behaviour may also reflect stockpiling of drugs. Oversupply leads to high unnecessary costs particularly among patients who are exempt from charges. This amount to 0.6% of the annual costs of prescribed drugs to outpatients in Sweden.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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## References

1. World Health Organization. Adherence to long-term therapies. Evidence for action. Geneva: World Health Organization; 2003 ISBN 924 154599 2
2. Andersson K, Melander A, Svensson C, Lind O, Nilsson JLG Repeat prescriptions – refill adherence in relation to patient and prescriber characteristics, reimbursement level and type of medication. *Eur J Public Health* 2005 Dec; 15(6):621–626

3. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity and applications. *J Clin Epidemiol* 1997; 50:105–116
4. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002; 288(4):462–467
5. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow-up study. *Heart* 2002; 88:229–233
6. Morningstar BA, Sketris IS, Kephart GC, Sclar DA. Variation in pharmacy prescription refill adherence measures by type of oral antihyperglycaemic drug therapy in seniors in Nova Scotia, Canada. *J Clin Pharm Ther* 2002; 27:213–220
7. Mojtabai R, Lavelle J, Gibson PJ, Sohler NL, Craig TJ, Carlson GA et al. Gaps in use of antipsychotics after discharge by first-admission patients with schizophrenia, 1989 to 1996. *Psychiatr Serv* 2002; 53:337–339
8. Hylan TR, Dunn RL, Tepner RG, Meurgey F. Gaps in antidepressant prescribing in primary care in the United Kingdom. *Int Clin Psychopharmacol* 1998; 13(6):235–243
9. Rudd P, Ramesh J, Bryant-Kosling C, Guerrero D. Gaps in cardiovascular medication taking: the tip of the iceberg. *J Gen Intern Med* 1993; 8(12):659–666
10. Haynes RB, Montague P, Oliver T, McKibbon KA, Brouwers MC, Kanani R (2001) Interventions for helping patients to follow prescriptions for medications. (Cochrane Review). In: *The Cochrane Library*, Issue 3, Oxford: Update Software
11. Heaton PC, Cluxton RJ, Moomaw CJ. Acetaminophen oversupply in the Ohio medicaid population. *J Am Pharm Assoc* 2003; 43:680–684
12. Frediani F, Cannata AP, Magnoni A, Peccarisi C, Bussone G. The patients with medication oversupply: clinical management problems. *Neurol Sci* 2003; 24(Suppl 2):108–111
13. Noyce PR, Huttin C, Atella V, Brenner G, Haaijer-Ruskamp FM, Hedvall M-B et al. The cost of prescription medicines to patients. *Health Policy* 2000; 52:129–145
14. LIF (Läkemedelsindustriföreningen), Fakta (2004) Pharmaceutical market and healthcare. LIF, Stockholm
15. Schafheutle EI, Hassell K, Noyce PR, Weiss MC. Access to medicines: cost as an influence on the views and behaviour of patients. *Health Soc Care Commun* 2002; 10:187–195
16. O'Brien B. The effect of patient charges on the utilisation of prescription medicines. *J Health Econ* 1989; 8(1):109–132
17. Lundberg L, Johannesson M, Isacson D, Borgquist L. Effect of user charges on the use of prescription medicines in different socio-economic groups. *Health Policy* 1998; 44:123–134
18. Westerlund T, Almarsdóttir AB, Melander A. Drug-related problems and pharmacy interventions in community practice. *Int J Pharm Pract* 1999; 7:40–50
19. (1997) Medical products agency, Vol. 10, §37–38. Sweden LVFS, Uppsala. ISSN 1101–5225
20. Al-Saffar N, Deshmukh A, Eid S, Carter P. Health beliefs and drug compliance of depressed patients in Kuwait. *J Soc Adm Pharm* 2003; 20:142–150
21. Apoteket AB (2002) Annual report, p. 42. Apoteket AB, Stockholm
22. Morris LS, Schulz RM. Patient compliance – an overview. *J Clin Pharm Therap* 1992; 17:283–295
23. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharm* 2000; 50:166–171
24. Casado JL, Sabido R, Perez-Elias MJ, Antela A, Oliva J, Dronda F et al. Percentage of adherence correlates with the risk of protease inhibitor (PI) treatment failure in HIV-infected patients. *Antivir Ther* 1999; 4(3):157–161
25. Information obtained from the drug statistics database of Apoteket AB, Stockholm
26. Isacson D, Olofsson C. Drugs up in smoke: a study of caseated drugs in Sweden. *Pharm World Sci* 1999; 21(2): 96–99
27. Ekedahl A, Wergeman L, Rydberg T. Unused drugs in Sweden measured by returns to pharmacies. *J Soc Adm Pharm* 2003; 20:26–31