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Research Article

Ghost pill: knowledge and awareness of this phenomenon among health care professionals

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ABSTRACT

Background: Slow release (SR) drug formulations associated with the passage of intact tablet like object in faeces sometimes known as the "ghost pill" have been in the market for many years. Anecdotal evidence suggests that few health care professionals are aware of this phenomenon. Our study aims were to find out what proportion of health care professionals was aware of the ghost pill phenomena and what drug formulations and specific drugs were associated with it.
Methods: A survey was conducted among health care professionals at three hospital sights in the West Midlands, UK. The subjects included doctors, nursing staff, pharmacists, and other allied professionals involved in patient care.
Results: A total of 321 health care professionals were included in the final analysis. Very few, 12.8% (41) have heard of the ghost pill phenomenon and a further 14 (4.4%) have come across of a patient who has experienced it. Only 13 (4%) correctly associated the phenomenon with SR drug formulations.
Conclusion: Our survey has shown that the ghost pill phenomenon, a normal outcome of a novel way of delivering orally taken SR drugs, is not well-known among health care professionals. Lack of awareness of it has implications to trainers, medical and nonmedical prescribers and nursing staff working with patients who are taking these medications. Lack of awareness among health care staff, may result in relevant information not being shared with patients at the time of prescribing or when patients enquires of it.

Keywords: Slow release, Ghost pill, Pharmacokinetic

INTRODUCTION

Taking medications orally is by far the safest and the most preferred method,[1] however; it has its own challenges for infants and young children, unconscious patients, people with mental health problems and those with chronic physical health problems. In the latter groups, medications may need to be taken by some more frequently each day for undetermined period of time. While taking medications orally several times a day has been linked with poor compliance, taking medications at a reduced frequency, once or twice a day has been associated with improved compliance.[2,3]

Improved pharmacodynamics and pharmacokinetic profiles of drugs taken orally are relevant not only to drug manufacturers, but also to prescribers and more importantly to those who are taking them. To improve drug delivery and the associated side-effect profiles, drug manufacturers have come up with several novel ways of delivering orally taken drugs such as fast disintegrating tablets,[4] sublingual method[5] and slow release (SR) formulations.[6] Throughout this article, SR would be used to encompass all terms used for orally administered modified or delayed release formulations.

Currently, SR drugs are widely prescribed both in psychiatry and other fields of medicine. However, despite clinicians using them over the years, anecdotal evidence suggests that few are aware that some have insoluble parts that can be visible to the naked eye when they are eventually passed out in faeces.[7] The passage of intact undigested or insoluble drug housing shells into faeces sometimes known as "the ghost pill" or "ghost-tablet"[8] occurs commonly with some SR formulations taken orally. It can be a source of anxiety, paranoia and mistrust for the uninformed patient and healthcare professionals.[7] Drugs associated with this phenomenon are widely available today. They are made in such a way that the active drug is released in a novel way, while the protective covering or certain undigested parts of the drug remains intact as the tablet or capsule traverses the gastrointestinal (GI) system. Lack of awareness of this seemingly normal phenomenon among clinicians may result in information not being shared with patients at the time of prescribing. As a result, some have become alarmed on seeing what looks like intact tablet or capsules in faeces.[7,9] We conducted a survey to assess the awareness of the "ghost pill" phenomenon among health care professionals in psychiatry and medicine. The term medicine would be used broadly to encompass all other specialty of medicine except psychiatry. The aim of this study was to determine the following:

1. What proportions of health care staff were aware of the ghost pill phenomenon?
2. How many of health staff have come across a patient who has experienced this problem
3. Staff knowledge of what drug formulations and specific medications related with the ghost pill phenomenon.

METHODS

A survey was conducted at three hospital sites in the West Midlands in the UK. Some of the hospitals host trainee teachings on weekly basis. A questionnaire specifically designed for this survey was used to collect the information. The authors distributed the questionnaires. It was given to staff members and trainees who were available during a nominated survey week. The survey was approved as a service evaluation by the Clinical Governance, Mental Health Directorate, Black Country Partnership Foundation Trust. Participants were drawn from medical and psychiatric services, trainees and non-trainees, nurses and doctors and other allied staff involved in patient care.

The questionnaire had brief introductory information about the ghost pill phenomenon, which stated, "It is understood that some medications taken as tablets or capsules have insoluble or non-digestible parts that are passed out in faeces and are known at times as ghost pills." After that brief information, participants were asked if they have heard of the phenomenon before. They were asked if they knew the drug formulations and specific medications that were associated with it. It was also enquired whether health care professionals read the patient leaflet information and the summary product characteristic (SPC) of medications patients were taking. We aimed to capture the views of many participants as possible.

RESULTS

A total of 432 questionnaires were distributed, 324 (75%) were returned and 3 were excluded due to missing relevant information. The remaining 321 that were included in the final analysis consisted of 188 (58.6%) females and 133 (41.4%) males. Broadly, 61.1% (196) were from mental health and 38.9% (125) from medicine. According to participant's profession, 161 (50.2%) were doctors, 122 (38%) were nursing staffs, 9 (2.8%) pharmacists, and 29 (9%) belonged to other categories (Table 1). The mean number of years at work was 8.19, with a range of 1-40. On average, 188 (58.6%) had worked <8 years, 87 (27.1%) had worked between 8-16 years and 46 (14.3%) had over 16 years work experience.

About 12.8% (41) claimed to have heard of this phenomenon before, however, only 14 (4.4%) of total sample have come across a patient who has had this problem in the past. Among those who have heard the phenomenon before, they sighted their sources as being from a patient 11 (3.4%), 3 (0.9) % by reading, 4 (1.2%) through case presentation and 18 (5.6%) sited other unspecified sources. There was association between the numbers of years at work and the likelihood of hearing of the ghost pill phenomenon. Those who have worked over 16 years, 23.9% have heard of the phenomenon (Pearson χ^2=6.3, d.f.=2, p=0.042). Significantly more non-trainees than trainees (Yates' corrected χ^2=5.85, d.f.=1, p=0.016) and mental health professionals than their medical colleagues members (Pearson χ^2=7.5, d.f=1, p=0.006)

Table 1: Demographic variables of participants.

Participants	Number	Percentage
Male	133	41.4
Female	188	58.6
Doctors	161	50.2
Nurses	122	38
Psych	196	61.1
Medicine	125	38.9
Trainees	130	40.5
Others	38	11. 8

appeared to have heard of the ghost pill phenomenon. Those working in mental health area were 3 times more likely to have heard of the ghost pill event than their medical colleagues (odds ratio: 2.96, 95% confidence interval: 1.32-6.4). Otherwise, there was no significant association of hearing of the phenomenon and gender, age group, doctor, nurse or others.

Overall 28 (8.7%) claimed that they knew why some drugs were associated with the ghost pill, however, only 13 (4%) correctly associated it with the SR formulation groups of drugs. Further still only 2 (0.6%) were able to mention a specific drug that has been associated with passage of empty intact shells in faeces.

The proportion of staff members that claimed to read the patient leaflet inserts "sometime" or "most of the time" was 87.5% and that reading the SPC of a drug at same frequency was 72.3%. Interestingly a significant large number 292 (91%) welcomed more information of the phenomenon.

DISCUSSION

A survey was conducted among psychiatric and medical staff members to assess their knowledge and awareness of the ghost pill phenomenon. Only small proportion, 12.8% have heard of it and a further smaller percentage (4.4%) have come across a patient who has experienced the problem. Though medicine as a whole appear to have more drugs that are associated with the passage of intact shells than psychiatry (Table 2) our survey however, showed that more mental health professionals appeared to have heard of the phenomenon than their medical colleagues. This may partly be explained by the observation that a significant proportion of the medical responders were trainees, who may not have worked long enough to acquire the experience.

The passage of intact shells occur on a daily basis for those who are taking drugs whose release mechanisms involve the passage of empty intact shell. However, it appears that only on some occasions, it becomes apparent to the person who is taking the drug. It is possible that some may have read the patient leaflet information and were aware of the incidents as being normal. However, for the uniformed patients, one incident more likely results in the individual becoming more vigilant. Without prior knowledge of the fact that this is normal for certain medications, this can result in the person being distressed, thinking that they have not been getting the prescribed dose of medications or thinking the drug may be faulty.[7,9]

Pharmaceutical companies provide a lot of information on each drug to professionals. This information is contained in the SPC for each drug. For patients, similar information is found in the patient leaflet information accompanying every dispensed drug. Most SPC and patient leaflets mention the passage of intact shell in faeces or stool if that is the known drug release mechanism. A significant number of health professionals claimed to read the SPC and patient leaflets, however, their clims were not backed by the results we observed. A recent review and newspaper reports highlighted the lack of awareness among health professionals and patients alike from all walks of life and different parts of the world. Patients can be distressed by seeing what looks like intact tablets or capsules, imagining that they have not been absorbing their medication.[7,9]

The SPC and patient leaflet insert should be better organized when highlighting the ghost pill phenomenon. Different drug companies place this information under different headings in the patient package insert as the following few examples illustrate: laboratories LICONSA[10] has the information on Venlalic XL under the heading "possible side-effect," whereas GlaxoSmithKline[11] has it under "how should I take Wellbutrin XL" for Wellbutrin XL. Janssen-Cilag[12] places same information on Lyrinel XL (Oxybutinin) under a subheading "how Lyrinel works" and Alphapharma,[13] has the information on Adefin XL under the heading "what Adefin XL is used for." Agreeing on the standardized format and where specifically to place this information may help in guiding patients where to look for this information given the bulkiness of the information already being given. The same variability can be seen in the information contained in the SPCs. The British National Formulary (BNF) has been noted to lack information on the ghost pill too.[7] The problems may be compounded given that a significant number of non-medical prescribers are on the increase. If similar information were provided in the BNF, it would allow clinicians and other prescribers to consult when needed.

It is acknowledged that SR formulations have several advantages over the immediate release (IR) formulations. Their novel release mechanisms allows them to be taken less frequently e.g. once or twice a day, providing a simplified dose regime and improved compliance.[2,14] Since they are released slowly over a prolonged period of time, they are less likely to be associated with GI side effect related with local irritation or sudden release of large quantity of drug in the GI tract e.g. stomach upset; hence they are more likely to be tolerated than the IR formulations.[15-17] SR formulations are associated with a slow steady rise of drug plasma concentration, remaining so over a prolonged period of time[15,18] resulting in less peaks and troughs variations of drug plasma levels than that observed with IR formulations. Hence in theory they are less likely to be associated with systemic symptoms related with rapid high peaks of drug plasma concentrations.[16] Having pH sensitive coating on some of them, allows targeted drug release delivery in specific areas of GI system.[19] Some drugs e.g. the opiate analgesia and some amphetamines carry the potential risk of being abused by drug addicts. However, the incorporation of anti-tamper mechanisms[20-22] and the use of SR formulations, which has been shown not to be associated with the anticipated drug euphoric rush, make SR less attractive for illicit use.[23] For drug manufacturers, SR formulations are a source of income

Table 2: Some brands that are associated with the passage of visible shells in feces.

Brand name®	Chemical name	Release mechanism	Indication
Acutrim	Phenylpropanolamine	Osmotic	Appetite suppressant
Adefin XL	Nifedipine	Osmotic	Hypertension
Alpress LP	Prazosin	Osmotic	Hypertension
Cardura XL	Doxazosin	Osmotic	Benign prostate hyperplasia
Covera HS	Verapamil	Osmotic	Hypertension
Ditropan	Oxybutynin	Osmotic	Overactive bladder
DynaCirc CR	Isradipine	Osmotic	Hypertension
Efidac/24	Pseudoephedrine	Osmotic	Cold medication
Glucotrol XL	Glipizide	Osmotic	Antidiabetic
Jurnista	Hydromorphone	Osmotic	Pain management
Lyrinel XL	Oxybutinin	Osmotic	Overactive bladder
Minipress XL	Prazosin	Osmotic	Hypertension
Procardial XL	Nifedipine	Osmotic	Hypertension
Sudafed 24 hr	Pseudoephedrine	Osmotic	Nasal decongestant
Teczem	Enalapril and diltiazem	Osmotic	Hypertension
Tiamate	Diltiazem	Osmotic	Hypertension
Tegretol XR	Carbamazepine	Osmotic	Epilepsy
Oxycontin	Oxycodone hydrochloride	Dissolution	Pain relief
Effexor XL	Venlafaxine capsules	Diffusion	Depression
Pristiq tablets	Desvenlafaxine	Diffusion	Depression
Venlalic XL tablets	Venlafaxine	Osmotic	Depression
Wellbutrin XL	Bupropion	Diffusion	Depression
Invega	Paliperidone	Osmotic	Schizophrenia
Concerta	Methylphenidate	Osmotic	ADHD
Ritalin SR tablets	Methylphenidate	Diffusion	ADHD
Focalin XR capsules	Dexmethylphenidate	Diffusion	ADHD
Venlafaxine extended release tablets	Venlafaxine	Osmotic	Depression

ADHD: Attention deficit hyperactivity disorder

and have also been used by drug companies to extend warrant or to provide exclusivity of the product in the market.[6]

It is important to note that SR formulations can be more costly than their counterparts. Some SR tablets are of large size and it is a challenge to swallow them. Like other tablets, SR tablets or capsules are not suitable for those with swallowing difficulties. Dose adjustment can be difficult with some. Because of how they are released, SR formulations are more likely to be exposed to first pass metabolism for a long period of time, suffering the risk of low serum levels.[24] When taken there may be a delay in reaching serum plasma levels, however, to compensate for this some SR formulations have combinations of both the IR and SR put together.[19] Beware of the risk of dose dumping and toxicity if the release mechanism fails or the drug is tampered with. For some individuals with pre-existing GI narrowing, SR can be a source of obstruction and pharmacobezoars.[25]

SR drugs utilises a number of drug release mechanisms resulting in the passage of intact shells in feces (Table 2). These include diffusion, dissolution and osmotic release or a combination of all of them.[6,7,26] It is important to note that not all SR drugs utilising diffusion or dissolution mechanisms are associated with the ghost pill problem; invariably though those utilising osmotic release mechanisms are. However, regardless of the release mechanism, the ultimate result is that an insoluble or indigestible visible part of the tablet or capsule is expelled intact in faeces. For more discussion on the release mechanisms of some of these drugs please see Siegel and Rathbone[6] Tungaraza et al.,[7] Sansom,[26] and Conley et al.[27]

Osmotic release mechanism relies on the principles of osmosis, where fluids movement occurs from low concentration to a higher concentration through a semipermeable membrane.[27] For the purpose of osmotic release in SR drugs, the membranes used allow one-way flow of fluids from the gut into the tablet. The table core is divided into chambers, the active chamber containing the drug of interest and the "push" layer housing a pharmacological inert, but osmotically active components.[19,27,28] Drugs utilising this model, are encased in a ridged compartment surrounded by a semipermeable

membrane. Once swallowed, fluid enters the tablet, creating pressure in the osmotic chamber. The resulting pressure pushes the active drug out through a leached or laser-drilled hole, providing a constant predetermine release of the drug. The structure of the tablet needs to remain intact for the mechanism to function, hence the release of the undigested part in faeces.

All SR medications come with the warning not to break or crush, chew or dissolve in water unless it is stated so, otherwise doing that my result in interference with the release mechanism and toxic levels of drug may be released. Remember that SR drugs have a large amount of medication than IR packed in one tablet to allow reduced frequency of taking medications.

Study limitations

Our study has some limitations. There were a large proportion of trainees, who may have not worked long enough to be aware of the problem or to come across a person who has experienced this phenomenon. However, our findings have implications to trainers, clinicians and pharmaceutical companies. Clinicians and trainees need to keep abreast with pharmacokinetic knowledge of SR formulations given that some drugs associated with the ghost pill phenomenon have been in the market for many years. Drug companies need to find a better way of sharing this information with patients and clinicians given that the current methods appear to have a limited desired outcome. However our study has a number of strengths. First, our study had a significant representation from other disciplines other than doctors providing a wide coverage of health professional experiences though their pharmacology training may be significantly different from that of medical doctors. Second, we surveyed frontline health care professionals who are in contact with patients.

CONCLUSION

We observed that though SR medications associated with the "ghost pill" are commonly prescribed, the phenomena itself remains less known among health care professionals. Reading the SPC and patient leaflet insert may help. However, drug pharmacokinetic training among doctors need to keep pace with advances in drug manufacturing technologies of our time.

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REFERENCES

1. Buxton ILO, Benet LZ. Pharmacokinetics: the dynamics of drug absorption, distribution, metabolism and elimination. In: Brunton LL, editor, Chabner BA, Knollmann BC, Associate editors. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 12th Edition. New York: McGraw Hill Medical; 2011: 17-40.
2. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296-310.
3. Kardas P. Comparison of patient compliance with once-daily and twice-daily antibiotic regimens in respiratory tract infections: results of a randomized trial. J Antimicrob Chemother. 2007;59(3):531-6.
4. Douroumis D. Orally disintegrating dosage forms and taste-masking technologies; 2010. Expert Opin Drug Deliv. 2011;8(5):665-75.
5. Smart JD, Keegan G. Buccal drug delivery systems. In: Wen H, Park K, editors. Oral Controlled Release Formulation Design and Drug Delivery. Theory to Practice. New Jersey: Wiley; 2010: 169-83.
6. Siegel RA, Rathbone MJ. Overview of controlled release mechanisms. In: Siepmann J, Siegel RA, Rathbone MJ, editors. Fundamentals and Applications of Controlled Release Drug Delivery. 1st Edition. New York: Springer; 2012: 19-46.
7. Tungaraza TE, Talapan-Manikoth P, Jenkins R. Curse of the ghost pills: the role of oral controlled-release formulations in the passage of empty intact shells in faeces. Two case reports and a literature review relevant to psychiatry. Ther Adv Drug Saf. 2013;4:63-71.
8. Anderson DT, Fritz KL, Muto JJ. Oxycontin: the concept of a "ghost pill" and the postmortem tissue distribution of oxycodone in 36 cases. J Anal Toxicol. 2002;26(7):448-59.
9. Malik S. Minister sends labs on a wild goose chase after pill pops out intact, 2012. Available from: http://www.tribune.com.pk/story/403679/look-but-dont-see-minister-sends-labs-on-a-wild-goose-chase-after-pill-pops-out-intact/[Last accessed on 2013 Jun 02].
10. Laboratorios LICONSA. Venlanic XL packge leaflet. Guadalajara: Laboratorios LICONSA, S.A; 2011.
11. GlaxoSmithKline. Wellbutrin XL package leaflet. London: GlaxoSmithKline; 2008.
12. Janssen-Cilag. Lyrinel XL package leaflet. Latina: Janssen-Cilag; 2012.
13. Alphapharma. Adefin XL package leaflet. Millers Point: Alphapharma; 2009.
14. Fleischhacker WW, Oehl MA, Hummer M. Factors influencing compliance in schizophrenia patients. J Clin Psychiatry. 2003;64 Suppl 16:10-3.
15. Verma RK, Garg S. Current status of drug delivery technologies and future directions. Pharm Technol Online. 2001;25(2):1-14. Available from: http://www.pharmanet.com.br/pdf/drugdelivery.pdf. [Last accessed on 2013 Jul 20].
16. Tang ESK, Chan LW, Heng PWS. Coating of multiparticulates for sustained release. Am J Drug Deliv. 2005;3(1):17-28.
17. Wilding IR. Coupe AJ, Davis SS. The role of gamma scintigraphy in oral drug delivery. Adv Drug Deliv Rev. 1991;7:87-117.
18. Lingam M, Ashok T, Venkateswarlu V, Madhusudan Rao Y. Design and evaluation of a novel matrix type multiple units as biphasic gastroretentive drug delivery systems. AAPS Pharm Sci Tech. 2008;9(4):1253-61.

19. Gabor F, Fillafer C, Neutsch L, Ratzinger G, Wirth M. Improving oral delivery. Handb Exp Pharmacol. 2010;(197):345-98.
20. Stanos SP, Bruckenthal P, Barkin RL. Strategies to reduce the tampering and subsequent abuse of long-acting opioids: potential risks and benefits of formulations with physical or pharmacologic deterrents to tampering. Mayo Clin Proc. 2012;87(7):683-94.
21. Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs. 2010;70(13):1657-75.
22. Davar N, Ghosh S. Oral controlled release based products for life cycle management. In: Wen H, Park K, editors. Oral Controlled Release Formulation Design and Drug Delivery. Theory to Practice. New Jersey: Wiley; 2010: 305-3119.
23. Spencer TJ, Biederman J, Ciccone PE, Madras BK, Dougherty DD, Bonab AA, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry. 2006;163(3):387-95.
24. Zhang H, Surian JM. Biopharmaceutic consideration and assessment for oral controlled relase formulations. In: Wen H, Park K, editors. Oral Controlled Release Formulation Design and Drug Delivery. Theory to Practice. New Jersey: Wiley; 2010: 33-45.
25. Simpson SE. Pharmacobezoars described and demystified. Clin Toxicol (Phila). 2011;49(2):72-89.
26. Sansom L. Oral extended release products. Aust Prescr. 1999;22(4):88-90.
27. Conley R, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. Curr Med Res Opin. 2006;22(10):1879-92.
28. Shamblin SL. Controlled release using bilayer osmotic tablet technology: reducing theory to practice. In: Wen H, Park K, editors. Oral Controlled Release Formulation Design and Drug Delivery. Theory to Practice. New Jersey: Wiley; 2010: 129-53.

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