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What are the nursing implications when using paliperidone prolonged release for people with schizophrenia

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What are the nursing implications when using paliperidone prolonged release for people with schizophrenia

Paliperidone prolonged release (PR) is a new product licensed for the treatment of schizophrenia. It is the active metabolite of risperidone, a drug that has been successfully used in the treatment of schizophrenia and mood disorder. Paliperidone PR has a unique pharmacological delivery mechanism that may incur benefits for particular patients diagnosed with schizophrenia. Studies investigating paliperidone PR are reviewed along with implications for its use by nurse prescribers and those nurses who monitor the use of medication for people with psychosis.

Keywords: medication, mental health, nurse prescribing

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Introduction

Many patients diagnosed with schizophrenia do not respond to treatment or they report unpleasant side effects and therefore stop treatment. The treatment of schizophrenia is less than satisfactory given that 75% of patients discontinue treatment within 18 months (Lieberman *et al.* 2005). This is why we must review all new agents to examine what benefits they may offer our patients.

Paliperidone prolonged release (PR) is a new agent licensed for the treatment of schizophrenia and shows promise in reducing psychotic symptoms, improving social functioning and being generally well tolerated (Davidson *et al.* 2007, Kane *et al.* 2007). Paliperidone PR is particularly suited for patients where hepatic issues form part of their formulation or where patients have chaotic compliance with medication.

This paper will review the relatively small number of research studies that have investigated the efficacy and tolerability of paliperidone PR. The limitations and challenges of this new drug are only just being understood in clinical practice. In this respect, further evidence is required before a stronger endorsement of the product can be made. The paper will outline what issues nurses need to be aware of if they were to prescribe paliperidone PR or for nurses who work as part of a team where paliperidone PR is prescribed by psychiatrists or general practitioners. This is important given that paliperidone PR is now licensed and available for use in the National Health Service (NHS).

Nurse prescribing

Prescriptive authority for mental health nurses in the UK first became established in 2003 (National Prescribing Centre 2005). Nurse prescribing is part of a general redevelopment of the nursing role and modernization of NHS care (Jones & Jones 2005). Two types of nurse prescribing exist. The first is supplementary prescribing which is a nurses who is suitably qualified can prescribe medication from a clinical management plan (CMP). The CMP is agreed with the psychiatrist and the patient (DH 2006a). The second is independent prescribing which is where a

nurse can prescribe medication without the need for an agreed CMP (DH 2006b).

Nurse prescribing is part of the redesign of healthcare services to make clinical decision making much more relevant to patients (Jones & Jones 2005, Jones 2006, 2008). The latest review on mental health nurse prescribing shows supplementary prescribing is as safe as prescribing carried out by psychiatrists (Norman *et al.* 2007). Medicines management is particularly lacking in mental health services with patients choosing not to take medication for a variety of reasons ranging from side effects to poor understanding of medication. One of the advantages of nurse prescribing is that it affords patients a different way to collaborate on choosing their medication based on individual side effect potentials (Jones & Jones 2008). Exploring the role of new medications when they become available for use is important for nurses who may prescribe them and to look at potential nursing implications in prescribing the drug.

Drug treatment and schizophrenia

The use of anti-psychotic medication to treat schizophrenia has been central to the patient's recovery since the 1950s (NICE 2003). Advances in psychopharmacology have led to a plethora of new drugs that differ in side effect profile but are broadly the same in terms of efficacy (apart from clozapine) (NICE 2003). Nurses who prescribe antipsychotic medication should do so by examining the evidence, drawing on clinical experience and responding to choices made by the patient.

Physical health of people with schizophrenia

People with mental health problems often have coexisting medical conditions. People with schizophrenia have higher rates of mortality compared with the general population: their life expectancy is reduced by 15 years (Brown *et al.* 1999). Diabetes, respiratory disorders, heart disease and obesity rates are all higher in people with schizophrenia and this is associated with antipsychotic medication (Newcomer & Haupt 2006). Although relatively less commonly diagnosed, liver disorders also require assessment and taking into consideration when planning treatment options. Nurse prescribers must be cognisant of monitoring physical health as part of their wider case management or prescribing role (Jones & Jones 2008). The impact of antipsychotic drugs on metabolic factors requires careful consideration, hence the importance of reviewing new drugs that are licensed for use.

Paliperidone PR

Paliperidone PR is a newly developed drug that is an active metabolite of risperidone, an atypical drug used for the treatment of psychosis. Paliperidone PR is similar in its pharmacological profile to risperidone although how it is metabolized by the liver is different. Risperidone is one of the older atypical agents proven to be efficacious for chronic schizophrenia (Peuskens & Group 1995).

Paliperidone PR is a controlled release oral formulation. Paliperidone PR is released from its capsule by osmosis. It builds up a gradual plasma concentration steady state within 5 days but has a therapeutic effect from day 1 (Marder *et al.* 2006). Paliperidone PR has a half-life of 23 h. This means a reduction in the peaks and troughs seen in immediate release oral medication. It also means that the drug dose the prescriber starts with is the expected therapeutic dose, thus in theory avoiding any initial dose titration.

Medication is metabolized by the liver and broken down by a series of enzymes called cytochrone P450. It is really important for nurses to understand the mechanism of metabolism because some patients range from slow to ultra rapid metabolizers. Knowing this information helps to determine the choice of medication that can be offered to patients. Particularly for paliperidone PR, it does not undergo significant breakdown by the liver with about 60% of the drug excreted unchanged by the kidneys (Vermeir *et al.* 2006).

Paliperidone PR binds to central dopamine type 2 (D2) receptors and serotonin 5HT2-A receptors (Karlsson *et al.* 2006). However, paliperidone PR binds less tightly to D2 receptors than risperidone. This may support the findings that side effect profile is different to risperidone, particularly the group of symptoms called extra pyramidal side effects (Seeman 2005).

Paliperidone PR is not majorly metabolized by the liver compared with other anti-psychotic drugs. The drug is mostly excreted, unchanged, through the kidneys (Vermeir *et al.* 2006). The route of excretion therefore has implications for patients who have renal disorders.

Drug distribution

The conventional method of immediate release of antipsychotic medication from a capsule or tablet tends to lead to large fluctuations in the drug plasma concentrations. The impact of this release method is twofold. First, when a peak and trough occur, therapeutic effect may also flow from bio-availability of the drug. There may be reduced therapeutic effect when a trough in plasma concentration is reached. Second, when peak concentration is reached, the patient may experience unpleasant side effects. This is why controlled release mechanisms become important to try and avoid the peaks and troughs of drug metabolism. Paliperidone PR is one of the first atypical antipsychotic drugs

to use an osmotic release-controlled delivery mechanisms (Conley 2006).

Receptor binding

It is important to understand how and why antipsychotic medication works. Antipsychotic drugs bind to receptors believed to be associated with too little dopamine or too much dopamine (Stahl 2006).

Receptors bind with the drug as the drug becomes available or metabolized by the liver. Fluctuations in binding to receptors are thought to be related to side effects and inconsistent therapeutic effect. Early studies have detected that when immediate release paliperidone PR is compared with controlled release paliperidone PR, receptor binding is significantly altered (Karlsson *et al.* 2006).

The osmotic delivery mechanism for paliperidone PR results in less peak and trough activity seen with other drugs as the drug is metabolized and excreted by the body (Karlsson *et al.* 2006). A minimal fluctuation in plasma concentration may be associated with less medication side effects. This effect is linked to the binding property of the drug. If the occupancy of D2 receptors exceeds 80%, adverse events may occur. However, the effect of a stable occupancy level of D2 receptors remains a theoretical construct. The latest dose finding study indicates that when paliperidone PR is prescribed at between 6 and 9 mg per day, D2 occupancy in the striatum and temporal cortex occurs at between 70% and 80%. This level of saturation is required for treatment effect (Arakawa *et al.* 2008).

Short-term studies looking at efficacy

There is very little research evidence documented about the efficacy of paliperidone PR. This is unsurprising given its recent entry into the market. A review of the literature was conducted and the following studies have been reviewed (Marder *et al.* 2006, Davidson *et al.* 2007, Kane *et al.* 2007, Kramer *et al.* 2007).

Kane *et al.* (2007) conducted a 6-week double-blind trial placebo and dose–response study in 630 adult schizophrenia patients. The control group received 6 mg, 9 mg or 12 mg doses. Surprisingly, the study included olanzapine as a control but did not report on its efficacy compared with paliperidone PR but did report on its adverse events. In total, 40% of patients discontinued the placebo drug because of perceived lack of efficacy compared with 16% for the paliperidone PR drug. The results were unclear if discontinuation was a dose–response effect. Interesting findings for the efficacy data suggest that improvement occurs from day 4 for the higher dose (12 mg) compared with day 8 for the lower dose (6–9 mg) (when compared with placebo).

In an earlier study reported by Marder *et al.* (2006), a change in symptom profile was reported earlier at day 4 for a dose of 6 mg when compared with 12 mg (day 15). Again, a similar design was used notably a 6-week double-blind randomized controlled trial comparing the efficacy of a 6 mg or 12 mg dose of paliperidone PR vs. placebo.

A similar 6-week double-blind dose–response study in 618 adult schizophrenia patients was carried out by Davidson *et al.* (2007).This time, patients received 3 mg, 9 mg or 15 mg of paliperidone PR compared with placebo. At the end of the 6-week period, 40% of patients taking 3 mg vs. 53% taking 15 mg achieved a change in baseline symptoms (when compared with a placebo response of 18%). This could mean you achieve a better response rate with the higher amount of drug.

It is interesting to look at how Meltzer *et al.* (2006) compiled a pooled analysis of the three trials noted above. Discontinuation because of lack of efficacy was reported as 40% in the placebo group and up to 17% in the paliperidone PR group. Discontinuation because of adverse events was similar across placebo. However, just short of a quarter of people discontinued the drug because of lack of efficacy and that is clinically important in everyday practice.

One study has been carried out looking at the safety and tolerability of paliperidone PR for people who were 65 years of age or older. Tzimos *et al.* (2006) carried out a 6-week placebo-controlled trial and concluded from the results that doses of either 6 mg or 9 mg were tolerable and proved efficacy to this age group.

There is a substantial deficit in evidence comparing paliperidone PR with other drugs, commonly referred to as head-to-head studies. Canuso *et al.* (2007) examined paliperidone PR vs. quetiapine in a 6-week double-blind placebo-controlled trial for patients with a relapse in their schizophrenia. The first 2 weeks of the trial were sole monotherapy and results indicated significant clinical differences in control of symptoms by day 5 in favour of the paliperidone PR group and at the 6-week end point. The difficulty with this study is that the average daily dose was higher than the recommended 6 mg daily dosing. At day 4 of the study, the paliperidone PR subjects were given a dose of 9 mg with the option of further increases to 12 mg. Higher doses incur greater risk of adverse events.

Long-term studies looking at efficacy

A long-term 12-month open label study investigating paliperidone PR was completed by Eerdekens *et al.* (2007). All patients who entered this trial had previously been enrolled on the trials described in the short-term trials above. A total of 628 patients were started on 9 mg although dose could

Table 1
lists the major areas where side effects occur for paliperidone PR

	3 mg	6 mg	9 mg	12 mg	15 mg
Insomnia	15%	11%	16–18%	12%	18%
EPSE	6–13%	3–10%	7–25%	10–26%	11–24%
Tachycardia	18%	18%	12–14%	22%	10%
Weight change	0.2			0.5	0.6
Somnolence	7%	4%	7–16%	8%	10%

Adapted from Marder *et al.* (2006), Kane *et al.* (2007), Davidson *et al.* (2007).
EPSE, extrapyramidal.

change, depending on symptom response from as low as 3 mg right up to 15 mg. In total, 21% of patients discontinued the trial because of patient choice and 7% because of adverse events. Symptom improvement occurred across the treatment dose range compared with placebo for the study duration.

Case studies

There has been only one case study reporting the use of paliperidone PR. This is a particular weakness in the appraisal of paliperidone PR for clinical use. The case study reported a possible case of neuroleptic malignant syndrome (NMS) when paliperidone PR was used instead of trifluoperazine and quetiapine. The patient was prescribed a 9 mg tablet for treatment of schizophrenia but by day 8, symptoms suggestive of NMS were present. The drug was discontinued and the symptoms of NMS abated (Duggal 2007).

What considerations are there to using paliperidone PR?

Nurse prescribers need to position paliperidone PR as one atypical drug among the others and to consider how the drug can benefit the needs of patients. Examination of the drug profile in terms of its delivery system and metabolism indicates certain types of patients that could be considered for the drug. Nurse prescribers need to be aware that all antipsychotic drugs have side effects and for some patients, they can be intolerable and for others, potentially harmful.

The prescribing of medication does not follow a predictable sequence. Some patients respond well to medication better than others. A host of reasons can be attributed to this, namely how the patient takes the drug and how the patient responds to it. The important point is for nurse prescribers to be aware of the side effects of certain types of medication and to identify potential areas of consideration for why one type of drug may be more suitable than others.

Side effects

Paliperidone PR is the active metabolite of risperidone and so some of the side effects presenting with the latter will occur but with less frequency and intensity. There are two main reasons for this. The first is the delivery mechanism and how the drug is distributed in a controlled way over a 24-h period. With other neuroleptic oral and depot drugs, the unequal distribution and plasma concentrations can cause a patient's movement disorders to vary considerably, particularly for older people (Zaleon & Guthrie 1994). In this regard, patients who respond well to risperidone but have intolerable side effects may fare better on a trial of paliperidone PR.

Table 1 indicates a range of dosing schedules. The summary of product characteristics states that 6 mg oral daily is the recommended dose (Summary of Product Characteristics 2007). However, all of the studies reported have used a variety of dosing schedules. It should be noted that 15 mg of paliperidone PR is not a licensed dose.

Extrapyramidal

The range of side effects labelled extrapyramidal (EPSE) ranges from a variety of movement disorders called tardive dyskinesia, akathisia, parkinsonian effects (Taylor *et al.* 2005). The trial by Kane *et al.* (2007) indicates a treatment emergent change in EPSE scores when the dose is raised to 9 mg and above. Up to 10% of patients will experience EPSE and this is related to a discontinuation effect seen in the 18-month trial conducted by Lieberman *et al.* (2005). In the long-term trial conducted by Eerdekens *et al.* (2007), up to 25% of patients experienced EPSE-related adverse events.

Metabolic syndrome

The trial by Kane *et al.* (2007) reported no significant change in glucose or lipids for any of the dosing schedules. There is no reported evidence that paliperidone PR leads to significant weight gain although patients do gain weight as

the dose of the drug is increased. When patients are prescribed 15 mg of paliperidone PR, mean weight gain can be 4.2 lb (Meltzer *et al.* 2006). This is relatively small and an important consideration for other drugs as weight gain is a particular problem and is associated with diabetes and coronary heart disease.

Hyperprolactinaemia

Paliperidone PR is associated with a raised prolactin level. Prolactin is a hormone that when above 600 mUL can lead to effects that mimick pregnancy in women such as breast enlargement. Even a starting dose of paliperidone PR 3 mg increases prolactin, particularly in females, and becomes increasingly more pronounced when doses of 15 mg are prescribed. Davidson *et al.* (2007) report that prolactin-related adverse events did not lead to study discontinuation although changes in prolactin were noted at day 15 of the trial and the study period was limited to 6 weeks. Female patients may be more likely to discontinue the drug as they experience amenorrhea as the months pass by.

The only dedicated study investigating the effects of paliperidone PR on prolactin has been carried out by Eerdekens *et al.* (2006). The study compared a dose of 12 mg paliperidone PR vs. 4 mg risperidone over a 6-day period. The study found that the same amount of prolactin secretion occurred with 12 mg paliperidone PR as it did with 4 mg risperidone. The problem with this finding is that a usual treatment dose of 6 mg of risperidone is required to acquire treatment effect and so this may correspond with a higher dose of required paliperidone PR. It is clear that paliperidone PR does cause prolactin elevation and will be a side effect to be managed in clinical practice (Citrome 2007).

Liver disorders

In the general population, it is estimated that 15% of people who consume large amounts of alcohol go onto develop liver disorder (Collis & Lloyd 1992). Early studies show that two-thirds of inpatients had a coexisting psychiatric disorder and alcohol-induced liver disease (Ewusi-Mensah *et al.* 1983). A recent study in the UK found that 24% of patients in the community who had a serious mental illness also used alcohol and/or drugs to a 'problematic' extent over the previous 12 months (Graham *et al.* 2001). Higher rates of alcohol misuse occur in people who suffer psychotic disorders (32%) (Menezes *et al.* 1996). This could be due to some form of shared glutamate mechanism disorder (Coyle 2006).

Liver disorders are also caused by highly infectious diseases like hepatitis and HIV. Hepatitis B and C is present in 23% and 20% respectively in people with serious mental illness (Rosenberg *et al.* 2001).

Nurses who prescribe medication or monitor the effects of medication may find a high prevalence of liver disorder in their patients who suffer from schizophrenia. Important considerations therefore manifest for the type of medication to be prescribed.

Liver disorders can result in impaired drug absorption, distribution, metabolism and protein binding of antipsychotic medication (Leipzig 1990). Certain types of antipsychotic medication are toxic to the liver, for example, chlorpromazine (Collis & Lloyd 1992). This is why medications that impair liver function or are metabolized by the liver may need to be prescribed at a lower, less therapeutic dose.

Antipsychotic medication is principally metabolized through the liver via CYP-450 pathways and other pathways such as CYP2D6. Considerable variation is present in a patient's ability to metabolize drugs and whether they are a rapid or a slow metabolizer. Up to 10% of white British population are poor metabolizers which means you need to give less of the drug for the desired effect (Bernard *et al.* 2006). For nurse prescribers, you may not know that the patient is a poor or rapid metabolier and one can only deduct this from clinical impression on side effects and lack of efficacy.

Paliperidone PR is not majorly metabolized by the cytochrome P450 pathway in the liver in the process called first pass metabolism. This implies less risk of interactions with drugs metabolized through this route (Vermeir *et al.* 2006). Thyssen *et al.* (2006) has found that the plasma concentration of paliperidone PR in moderate hepatic impairment is the same as people who have a healthy liver function.

Clinically, this offers benefits for people with schizophrenia. An impaired liver function test (LFT) means that drugs may not be metabolized as expected leading to a build up of the drug in the system. For example, drugs such as aripiprazole are metabolized by CYP2D6, an enzyme used by the liver to metabolize the drug (Taylor *et al.* 2005).

The reasons for an impaired LFT may be due to alcohol or drug misuse. Clinically, this may translate to impaired liver function and a reduced ability to metabolize drugs when compared with normal patients. Patients may have difficulty in processing waste products. Patients may develop jaundice, have an increased clotting time, develop ascites. However, an LFT by itself is a poor indicator of the capacity of the liver to metabolize drugs (Taylor *et al.* 2005).

Nurse prescribers do not need to worry about the effects of prescribing paliperidone PR for moderately impaired hepatic systems, nor the effect that paliperidone PR has on the metabolism of other drugs metabolized by the liver.

Paliperidone PR therefore offers clinical benefits over and above other antipsychotic agents in this respect.

Impaired kidney function

There is no useful statistic for the prevalence of renal impairment for people who have schizophrenia. However, nurses need to be mindful of impaired renal function and the way the kidneys metabolize and excrete certain drugs.

There appear to be no renal drug to drug interactions with paliperidone PR that may affect its excretion from the renal tube (Thyssen *et al.* 2006). However, the drug is excreted in the renal system and so nurses need to be aware of impaired renal function. What this means is that patients may not be able to excrete paliperidone PR at the same rate as people without renal impairment. The drug may then build up into a higher concentration and lead to a higher chance of developing side effects.

A test to determine renal impairment is the glomerular filtration rate. Nurses need to order a test for creatine clearance and to be able to determine a mild, moderate or severe serum creatine clearance result (Taylor *et al.* 2005). In total, 60% of paliperidone PR is excreted by the kidneys and so the dose may need to be prescribed at smaller quantities in mild renal impairment. Patients who present with moderately impaired kidney function disorder should avoid being prescribed paliperidone PR.

Sleep maintenance

The promotion of a regular sleep pattern is important for recovery from an episode of schizophrenia and to promote long-term management of the illness. The prodromal aspect of schizophrenia itself can manifest as sleep disturbance (Chemerinski *et al.* 2002). Luthringer *et al.* (2007) tested the effects of 9 mg of paliperidone PR on sleep architecture in a 14-day placebo-controlled trial in 36 patients. Interestingly, paliperidone PR was shown to increase the time people spent asleep and a reduction in the time of getting off to sleep. In an earlier study by Luthringer *et al.* (2006), paliperidone PR did not worsen somnolence during the day when compared with patients receiving placebo, a finding supported again by the later study (Luthringer *et al.* 2007).

Many anti-psychotic drugs confer sedative properties during the day, notably olanzapine and quetiapine (Stahl 2006). Paliperidone PR may have a clinical advantage over these drugs for people who have difficulty getting off to sleep and staying asleep without hamper daytime functioning. However, nurse prescribers need to consider that one of the most frequent side effects of paliperidone PR is somnolence, commonly seen as daytime sedation (Canuso *et al.* 2007). This may be a side effect that emerges over a longer time period.

Concordance

Trial data and clinical experience tell us that patients do not take medication as prescribed for a whole number of reasons. In total, approximately three-quarters of patients in a large United States Government sponsored trial discontinue their medication within 18 months of starting it (Lieberman *et al.* 2005) and these results have been replicated in Europe (Jones *et al.* 2006). How patients tolerate medication is a large concern for them. This is why we must offer our patients a choice over what medication they wish to be prescribed for them if they have schizophrenia.

One of the benefits of paliperidone PR lies in its distribution. The controlled release mechanism of the drug leads to small fluctuations in its peak and trough plasma concentration than with immediate release paliperidone (Karlsson *et al.* 2006). This means that patients, who occasionally forget to take medication, may do so without necessarily leading to low plasma levels and therefore risk of relapse (Davidson *et al.* 2007).

Costs of prescribing paliperidone PR

Nurse prescribers need to consider that drug costs amount to 2% of total costs of caring for newly diagnosed people with schizophrenia (Guest & Cookson 1999). Paliperidone PR is a derivative of risperidone. Patients receive around 32% of paliperidone PR if they take risperidone (Dollery 1999). A significant barrier to the prescription of this drug will be the costs of prescribing it given that risperidone is available in a generic formulation (Citrome 2007). The choice for patients, however, may be a more tolerable side effect profile. This may bring about better concordance and reduced costs further incurred through relapse.

Case study research

There is increasing recognition that nurse prescribers are becoming adept at describing the method of prescribing along with particular drugs used to treat the patient (Jones & Jones 2008). Case studies serve this process extremely well. The lack of case material on paliperidone PR is a particular deficit in evaluating the effectiveness of the drug, as opposed to its efficacy. Case study research also highlights actual side effects that can be placed in context. The efficacy of the drug requires extensive head-to-head, naturalistic research.

This paper has considered types of patients that may benefit from paliperidone PR. Table 2 identifies these patients by examining the available evidence. It would be productive for nurse prescribers to begin case studying the use of paliperidone PR to these patient types.

Table 2
Patient profile

Patient type	Cause
Patients with liver disorders	Infections, alcohol dependence
Patients who may have drug–drug interactions	Impaired liver and drugs competing for limited metabolic processes
Patients who have low metabolic processes	More drug required and so increased likelihood of side effects
Patients where concordance is poor	Once daily dosing for chaotic users

Further controlled trial research testing out sub-types of patients listed in Table 2 would be necessary for stronger conclusions to emerge from this paper. Case material would help to put substance to the types of patients that may benefit from the drug.

Conclusion

This paper has considered the latest antipsychotic drug to become available for the treatment of schizophrenia. Very few studies have been completed and all but one are short-term. The results demonstrate that the new drug is significantly better than placebo. This is expected given that paliperidone PR is risperidone but in a purer form without all the other derivatives of risperidone. There has only been a single head-to-head trial with quetiapine and none with its parent compound risperidone. Trials to date have been funded by the makers of the drug and so bias in the reporting of results also needs to be considered. Weakness of the data set is further compounded by the relatively few trials completed before the drug has come onto the formulary.

The dose-treatment response evidence is inconclusive. We need to understand more about the lowest possible dose to achieve symptom control. Paliperidone PR has a favourable dose side effect profile when given at low doses. A more consistent release of the drug may reduce occupancy saturation exceeding 80% and this may be linked to the limited first pass metabolism. We need 'real world' clinical evidence to back up what is the true dose to achieve symptom control while minimizing side effects. The unique delivery mechanism of paliperidone PR may confer benefits in reducing the fluctuation in binding activity when compared with other drugs. Case study profiles will help to draw out these cases.

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