

Access to experimental drugs: legal and ethical issues of paternalism

David Badcott and Joy Wingfield begin a new series highlighting issues in healthcare ethics and law by considering the case of a dying child

The science column in *The Times* of 21 May 2007 focused on the story of a four-year-old American girl, Penelope London, dying of an aggressive brain cancer. In the US, the age of majority is determined by state law and is usually 18, 19 or 21 years. Thus, as in the UK, the law recognises that a child of four years of age does not possess autonomy in the sense of being able to make his or her own informed decisions. Paternalism in its most benign form means that parents make decisions for their children. Penelope's father, John London, believed that treatment with SVV-001 (Seneca Valley Virus — a naturally occurring virus able to kill cancer cells) being developed by the small biotech company Neotropix Inc might offer some hope for his daughter.

Although Neotropix had received Food and Drug Administration approval to begin clinical trials, the company refused to make supplies available to Penelope because of concern that the drug might not be safe for her (the toxicological data were inadequate and inappropriate). Furthermore, there was a perceived risk that if the child received the drug but nevertheless died this could critically damage the viability of a small, low resourced company (its clinical trials had previously been put on temporary hold following the death of a patient that was subsequently demonstrated to be from cancer and not from the treatment) as well as delay prospects of treatment for others.

The FDA had, nevertheless, indicated, as reported in the *Wall Street Journal* (1 May 2007) that it "would not hold a company accountable for the death of a very sick person receiving therapy as a desperate effort". It also stated that the notion that the FDA would halt trials over a death in such circumstances is "more of a myth or an urban legend". But, in the event, this announcement was not tested in the courts because Penelope died on 19 May 2007.

Ethical considerations

There are a number of relevant ethical principles when considering this story:

- Autonomy versus paternalism
- Autonomy as the basis for informed consent
- Parental proxy for a child lacking autonomy
- The common good (through traditional clinical trials) versus individual risk

There is much contemporary support for the concept of autonomy as a fundamental

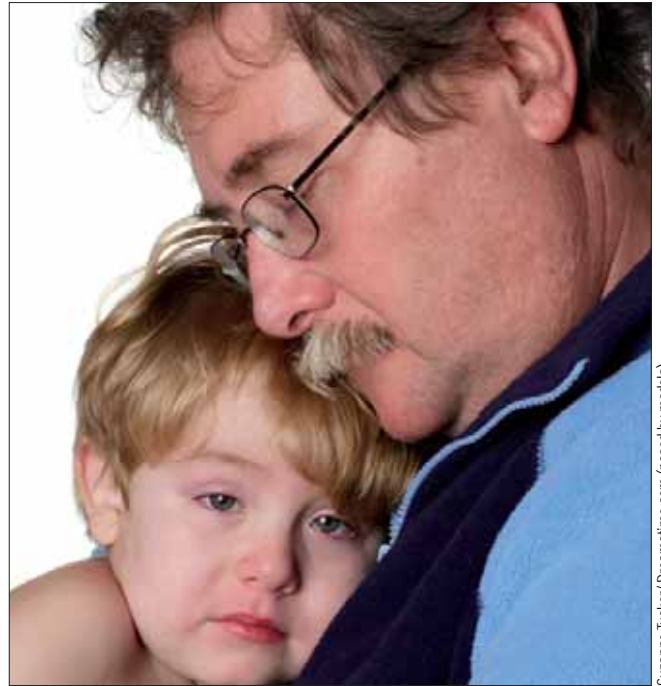
principle. It underpins many aspects of healthcare, and is cited in the pursuit of national and, particularly, global human rights (especially those that also touch on concepts of justice and fairness). Consideration of autonomy is often pivotal in decisions concerning the treatment, welfare and interests of individuals. Definitions of autonomy are somewhat varied but generally centre on the right of competent human beings to be allowed to make their own decisions according to their own wishes, life plans and goals. Autonomy can be compromised in several ways:¹

- Intellectual deficiency or impairment
- Ignorance of relevant factors
- Inability to appreciate the relevance of autonomy
- Emotional instability
- Temporary incapacity

It is recognised in law that children, particularly young ones, are not autonomous in the full sense because they do not have an ability to assimilate relevant information and take informed and rational decisions. In other words, they are not competent. Consequently, children's autonomy is circumscribed as with mentally incompetent adults. But unlike the latter (and excluding those temporarily impaired by mental illness) a child's autonomy develops progressively over time into adulthood.¹ For this reason, healthcare workers must take into account the age, ability and relative competence of the individual child.

Paternalism can be seen as a barrier to the exercise of autonomy. We say that an action is paternalistic when an individual intervenes, prevents someone from doing something or causes someone to do something against his or her will. In healthcare this extends to taking decisions on someone else's behalf with-

David Badcott is a member of the Centre for Applied Ethics, Cardiff University, and Joy Wingfield is professor of pharmacy law and ethics at the School of Pharmacy, University of Nottingham



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out their consent or involvement. As a parent of a four-year-old child, Mr London was entitled to take decisions on that child's behalf and to press for what he considered to be the only potential life-saving treatment for her.

However, there are several issues that would need to be taken into consideration. For example, the intervention may have been futile. This expression is used commonly where a patient's prognosis is so poor that treatment would be pointless. Although this was, perhaps, not strictly the case here, the treatment was unproven or might not only have caused adverse effects but might even have curtailed the child's life. There is no clear answer — we cannot know whether or not the drug would have proved to be effective or harmful — but we can appreciate that hope born out of a sense of desperation is a powerful motivator, albeit one in which rational and impartial judgement may be difficult to maintain.

We can also ask what factors might be taken into account in allowing parents to take decisions on behalf of their children. Are they (the parents) sufficiently well informed to give proper consent? Are they able to weigh possible benefits against potential harm? And can they reliably consider the child's best interests? Finally, it could be argued that Mr London was acting against the common good because seeking privileged "individual" access to SVV-001 outside of a properly constituted clinical trial (even though the FDA's stance

was not obstructive) could hamper the drug's further development.

Legal considerations

It is not only people who can be paternalistic. Most of our legislation is paternalistic in that the state takes decisions on behalf of the general population to ban certain activities or restrict access to certain products. All of our medicines, poisons and Controlled Drugs law is, in fact, largely aimed at avoiding either self-harm or harm to others. But should the law prevent people from taking risks they voluntarily accept? The philosopher John Stuart Mill, although supportive of legislation intended to prevent harm to others, argued strongly against the use of the law to prevent self-harm.² In the case of Penelope London, her father was demanding access to an unproven treatment. A more usual scenario that has come before the English courts occurs where parents reject proven treatment for their child on grounds of religious belief, such as the refusal of blood transfusion by Jehovah's witnesses. Here, the courts can (and often do) override such objections to enable treatment to be compulsorily delivered, but almost always in the knowledge that treatment has a high probability of success. So there is a limit to parental choice.

In addition, the courts cannot compel a manufacturer to supply against its wishes — an individual's right to pursue his or her own autonomous ends should not be at the expense of, or infringe third party autonomous rights (eg, those of Neotropix to refuse supply). Nor for that matter, could a physician be compelled to administer an experimental drug to a patient against his or her judgement. In the words of Vince and Petros, "doctors are not . . . ethically obliged to provide any treatment they believe is not beneficial to the patient and, indeed, are ethically obliged to avoid such interventions".³

So the law generally errs on the side of paternalism and creates statutes or makes judgements to protect people from themselves. There are several examples, however, where pharmaceutical companies have risked liability for harm when the patient voluntarily accepts the risk of using an unlicensed medicine. Furthermore some people do not readily accept the current status of the rigid checks and controls on access to potentially life-saving medicines. Some of the barriers have been successfully confronted in the US by pressure from the AIDS lobby. Research on potential antiviral treatments reflected a marked change in the attitude to regulatory orthodoxy. AIDS sufferers challenged, in particular, the conventional wisdom of the double blind placebo controlled trial. Time was not on their side — they wanted active experimental drugs that could possibly save their lives and were prepared to accept any consequential risk. Coupled with this was the impact of the large numbers who could be organised to protest and lobby. Roy Porter noted that "people-with-AIDS (PWA) possessed a daring born of desperation and out-

rage. PWAs were middle class, politically savvy . . . highly educated".⁴ The action group, the AIDS Coalition to Unleash Power (ACT-UP) was initially set up to lobby "for rapid approval and affordable access to Burroughs Wellcome's (antiviral) AZT".⁵

The net result was a rethinking and acceleration of trial procedures, particularly in the US where the lobby was most influential, to facilitate early access for those with terminal illnesses, not only AIDS but, eventually, advanced breast cancer, Parkinson's disease, Alzheimer's disease and juvenile diabetes. Also in the US, a patient advocacy group, the Abigail Alliance for Better Access to Developmental Drugs is lobbying and pursuing legal action to allow terminally ill patients access to successful post phase I candidate treatments, thereby bypassing the normal regulatory system. In 2006, the alliance won its argument in the US Court of Appeal, that being deprived of medicines undergoing trial that could save people's lives violated their constitutional rights. The FDA subsequently appealed this decision, apparently motivated by concern that wider access to experimental drugs could undermine general preparedness to participate in clinical trials and thus damage the means of establishing generalisable safety and efficacy data. The case was decided in favour of the FDA in 2007 by a majority of eight to two on the grounds that "the alliance had not provided evidence of a right to procure and use drugs that is deeply rooted in our nation's history and traditions".⁶ And, most recently, the Supreme Court declined to consider whether terminally ill patients have a right to be treated with experimental drugs not yet approved by the FDA.⁷

In Canada and Europe, the concept of "compassionate use" is now well established. A European directive (2004) allows member states to authorise the use of products already in clinical trials, or subject to review before a marketing authorisation, to be given to patients suffering from a life-threatening disease and for whom no authorised medicine is available. In England, the prospect of death from aggressive forms of breast cancer led, in 2006, to an almost politically driven intervention in the availability of Herceptin, ahead of the careful consideration usually associated with the licensing process.

There is nothing to stop anyone from self-medicating with anything they can lay their hands on for any ailment, serious or otherwise, provided that no laws have been broken to obtain it. Folk remedies from many sources abound and, provided that the seller makes no therapeutic claims and the substance or product is not frankly harmful, doubtless many members of the public experiment with such "remedies" and may even enjoy an element of placebo or other benefit. But where major life-threatening illnesses, such as cancer, are concerned, the law tends to intervene.

Self-medication, at least to the extent of placing medicines on the open market, is restricted to relatively safe, low potency products with a well established therapeutic

profile. The law also limits (paternalistically some might say) the opportunity for self-harm and suicide, by restricting pack sizes and dosage of oral analgesics for over-the-counter sale. But even the present day regulatory requirements do not entirely guarantee complete safety. The withdrawal of Vioxx (rofecoxib) in 2004 from sale worldwide after some seven years' post-marketing availability and the horrific experiences of the healthy volunteers in the phase I study with the monoclonal antibody TGN1412 highlight the risks and inadequacy of some existing procedures in the early stages of drug testing.

So caution and restriction appear to be well justified because freedom from adverse effects cannot be guaranteed. Acts of Parliament intended to control the testing, licensing and availability of pharmaceutical medicines generally serve the common good, defined as "maintaining conditions and achieving objectives that are similarly to everyone's advantage",⁸ and protect members of the public, as far as is possible, from undue harm. Availability of pharmaceutical medicines is controlled by a series of gatekeepers, from the medicines regulators and those who issue prescriptions to those who dispense them and ensure that patients are clear on directions for use. On this account, being gatekeepers of medicines and other healthcare resources can be viewed as a necessary application of state power.

Relevance to pharmacy

It is, of course, reasonable to ask whether these ethical and legal issues are relevant to pharmacists. The simple answer is "almost certainly" for those pharmacists involved in regulatory affairs, clinical trials or some aspects of research and development. But all pharmacists should appreciate some of the wider aspects and implications of those laws relevant to pharmacy that, by and large, we may tend to take for granted. Legal paternalism, in some form or another, is here to stay and has a strong bearing on all areas of pharmacy practice, whether we recognise it or not.

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