Winter 2013

Newsline

HPS Pharmacies

HPS On-site at Sydney Southwest Private Hospital, Providing Chemotherapy Services to the South Western Community of Sydney

Plus:

HPS Pharmacies Announces Inaugural Enterprise Agreement, and Expands Specialist Services to SA Ambulance Service's Rural Sites

HPS Pharmacies

Sponsorship

HPS Pharmacies would like to thank and acknowledge the continual support of their sponsors.

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Cover Image
(Left to right) Megan Farnsworth, Partner/Regional Operations Manager – QLD/NSW at HPS Pharmacies, with Julie Cohen, Nurse Unit Manager Oncology at Sydney Southwest Private Hospital

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Message from Tony Wyatt CEO

As we reach the midpoint of 2013, many advances have been realised for both HPS Pharmacies and the pharmacy industry as a whole.

In May, the Federal Government announced a $30 million investment back into cancer treatment to alleviate the effects of price disclosure, recognising the critical need for funding support around chemotherapy reconstitution. As a founding member of the Community Pharmacy Chemotherapy Service Group, HPS Pharmacies welcomes the Federal investment, delivering much needed confidence back into chemotherapy dispensing returns within the private sector.

HPS Pharmacies is committed to continuing to meet the needs of our clients and their patients in delivering their much needed oncology services, and looks forward to further announcements by the Federal Government around chemotherapy funding in the future.

The end of financial year also marks a change to the HPS Pharmacies' Board. Long-term members, Kirsten Boyce, Partner/Director of Strategic Management and Megan Farnsworth, Partner/Regional Operations Manager – QLD/NSW, have completed their terms on the Board, and nominations held for the available positions. Accordingly, it is with great pleasure I announce that Tin Huynh, Partner/General Manager – Hospitals, has been elected a vacated Board Member position.

HPS Pharmacies would like to thank retiring directors, Kirsten and Megan for the dedication and time committed to the Board over the past seven years.

Looking to the financial year ahead and the successes and growth it promises to bring, HPS Pharmacies Strategic Plan was revisited at The Partner Strategy Summit held in May. The Summit is an opportunity for the congregation of equity partners and the Executive Team to invest significant energy, time and focus on shaping the HPS Strategic Plan in line with changing client needs, industry movements and market opportunities.

This year's summit highlighted a wealth of opportunities and strategic initiatives for HPS Pharmacies in consolidating its future success and longevity for our clients and within our industry.

Tony Wyatt
Partner / Chief Executive Officer

Message from Steve Yeo COO

HPS Pharmacies has experienced a huge amount of success in its business/corporate development performance over the last 12 months, securing a number of large client contracts and solidifying its position as the leaders of pharmacy service provision in the Australian market.

Of particular significance for this period is the successful negotiation of the inaugural Enterprise Agreement for HPS Pharmacies' pharmacist community. This momentous agreement ensures a strong foundation for new client contracts moving forward as an employer of choice within the industry, and represents HPS' commitment to investing in its integral employee network.

Further to the announcement in February regarding the unveiling of HPS Pharmacies' new corporate logo, from July clients will also begin to see a refresh to our pharmacy staff with the introduction of a new uniform, rolled out over a 12 month period. The design delivers consistency to our modern brand, and will provide differentiation and unique identification of pharmacy roles for easy recognition by our clients. This investment is again reflective of HPS Pharmacies' pledge to deliver a high performing culture that encourages its staff members to flourish.

I would also like to take this opportunity to recognise the staff of HPS Pharmacies' Modbury site, whose workplace was recently inundated with flooding.

The staff members conducted themselves with professionalism, patience, and positivity in ensuring that pharmacy services to the patients of Modbury Hospital were maintained during the upheaval, which was of great appreciation to the client.

On behalf of the business I would like to applaud the staff for their efforts.

An equally exciting phase of growth is forecasted throughout the next financial year, with many new innovations, strategic foundations, and the opening of several new pharmacies coming to fruition.

We move forward into a rewarding and prolific environment for the business, guaranteeing our vision of being industry leaders remains at the forefront of our endeavours in delivering the highest quality pharmacy services to our valued clients.

Steve Yeo
Chief Operating Officer

This page: (left to right) May Valdez, Registered Oncology Nurse at Sydney Southwest Private Hospital, with Anjana Rao, Pharmacy Manager, at HPS – Sydney Southwest.

Cover page (left to right): Megan Farnsworth, Partner/Regional Operations Manager – QLD/NSW at HPS Pharmacies, with Julie Cohen, Nurse Unit Manager Oncology at Sydney Southwest Private Hospital.

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HPS On-site at Sydney Southwest Private Hospital

In 2012, HPS Pharmacies excitedly announced its successful resigning with Australia's leading healthcare provider, partnering with Healthscope for another six years. This integrated partnership has been further strengthened with the addition of another Healthscope hospital to HPS Pharmacies growing portfolio of clients.

HPS Pharmacies' newest on-site pharmacy was recently opened at Sydney Southwest Private Hospital, and is purpose-built to support and deliver specialist services to the new oncology unit.

Tin Huynh, HPS Pharmacies' Partner/General Manager – Hospitals, says "having an on-site pharmacy with sterile compounding capabilities will allow HPS Pharmacies to deliver a quality, efficient, timely and cost effective oncology pharmacy service. The rest of the hospital will also benefit from better access to pharmacy services, especially for discharging patients and inpatients."

Sydney Southwest Private Hospital's Acting General Manager, Michelle Stares, is enthusiastic about the recent development, and the benefits that accompany a comprehensive on-site chemotherapy service delivered direct to their patients.

"Sydney Southwest Private Hospital's oncology clinic provides a necessary service within the local health district, allowing privately insured patients to avoid the extensive waiting periods currently experienced at the public hospital," says Michelle.

"Our new partnership with HPS Pharmacies will provide a seamless experience and specialist advice for patients undertaking chemotherapy treatment."

HPS Pharmacies' National Oncology Manager, Zeyad Ibrahim, has been consulting with the hospital from the outset to ensure a smooth transition of services, and emphasises the high level of specialisation and expertise HPS Pharmacies provide in oncology.

"Oncology units require a comprehensive and dedicated clinical service to cater for cancer patients, and the vulnerabilities and risks they acquire due to their disease and potent treatment need," says Zeyad.

"HPS Pharmacies has assisted in designing the patient care system that is currently adopted at the unit. The system is all-encompassing from the timely and accurate supply of chemotherapy, to patient education and providing advice to assist clinicians in the decision-making process."

The hospital has quickly experienced positive results with HPS Pharmacies on-site. Anjana Rao, HPS Pharmacies' Pharmacy Manager at Sydney Southwest has been remotely situated at the hospital since the opening of the oncology unit, and now manages services from the on-site pharmacy.

"Working with the staff, doctors and patients of Sydney Southwest has been rewarding. Our pharmacy services are an important part of patient treatment, and are of great value to the nursing staff and the referring medical oncologists. Having an on-site pharmacy will assist in maintaining and tailoring our service provision in line with the growth of the oncology clinic," says Anjana.

The area of oncology has been a focus for HPS Pharmacies over the last 12 months, and the opening of its first oncology compounding pharmacy in New South Wales signifies a milestone for the business within this growing market, and foreshadows many exciting developments within the oncology arena moving forward.

Tin Huynh says, "HPS Pharmacies is thrilled to be providing on-site oncology pharmacy services to Sydney Southwest Private Hospital. The introduction of an on-site pharmacy is an excellent example of both organisations working together to ensure patients are receiving the highest quality of care when they are admitted into a Healthscope hospital serviced by HPS Pharmacies."

> *"Our new partnership with HPS Pharmacies will provide a seamless experience and specialist advice for patients undertaking chemotherapy treatment."*
>
> – Michelle Stares, Acting General Manager, Sydney Southwest Private Hospital

Expanding Specialist Services to SA Ambulance Service's Rural Sites

SA Ambulance Service (SAAS) is an integral part of the South Australian health system, providing medical assistance, treatment and transport, delivering the highest quality of patient care to the people of South Australia.

SAAS has been a valued client of HPS Pharmacies for many years, and recently renewed their service contract to extend pharmacy services to their 20 rural sites across the state.

Agnes Gower, Partner/Site Manager – Alexander Avenue at HPS Pharmacies is proud to have enjoyed a strong working relationship with SAAS that has spanned over 20 years.

"The long-standing relationship is based on a mutual respect, and focuses on the provision of a highly professional and tailored pharmacy service," she says.

"HPS Pharmacies has always been responsive and understanding of the unique service offered by SA Ambulance Service, and take a collaborative approach to the delivery of pharmacy services."

Peter Hayball, Senior Pharmacist at SAAS, explains HPS Pharmacies' determination to deliver more than a generic pharmacy service.

"HPS Pharmacies employ highly motivated staff that are willing to go above and beyond. Ian Tindall, one of HPS Pharmacies' Senior Pharmacists, shares a rich history with SAAS, and has extensive experience having previously been involved in delivering consultancy services to the paramedics."

"SA Ambulance Service benefit from unlimited advice and expertise in the provision of specialist pharmaceuticals," says Ian Tindall.

"HPS Pharmacies has an extensive distribution network, ensuring timely delivery to meet the client's unique needs."

Peter says HPS Pharmacies are able to provide a more tailored range of products that are able to meet SAAS's requirements as a state-wide provider of services in the pre-hospital environment.

"At SAAS we have redesigned our controlled substances system, from ordering through to delivery, and ultimately patient use. HPS Pharmacies are an integral part of this process in assisting us to get controlled substances in a timely and efficient manner to ambulances across South Australia."

Agnes Gower believes the relationship's success can be attributed to the collective and varied experience within the healthcare sphere.

"We have a mutual understanding of each other's business models and requirements, and the factors influencing the provision of an efficient and effective pharmacy service," she says.

Peter is enthusiastic for the future of SAAS in engaging with HPS Pharmacies, and is currently in discussions to expand the range of specialist products that are sourced from HPS Pharmacies, given the success of previous ventures of this nature.

"We are once again delighted to work with HPS Pharmacies in a working relationship that is highly valued across SAAS. As the emergency ambulance arm of SA Health, we at SAAS are committed to patient safety and ensuring our patients receive treatment of the highest order that is evidence-based and consensus-driven."

This sentiment is further highlighted by Dominic Coppola, HPS Pharmacies' Partner/Regional Operations Manager – SA/NT.

"This contract represents the reuniting of two healthcare organisations whose visions are well aligned. Our service model has transitioned over time to adjust for the changing needs of SA Ambulance Service, and HPS Pharmacies is dedicated to continuing to deliver a responsive and high quality pharmacy service, underpinned by HPS Pharmacies' knowledge and service specialities. We look forward to a fruitful future with the Service."

> *"HPS Pharmacies are an integral part of the process in assisting us to get controlled substances in a timely and efficient manner to ambulances across South Australia."*
>
> – Peter Hayball, Senior Pharmacist, SA Ambulance Service

This page: (left to right) Luke O'Callaghan, Extended-Care Paramedic at SA Ambulance Service, with Agnes Gower, Partner/Site Manager – Alexander Avenue, and Dominic Coppola, Partner/Regional Operations Manager – SA/NT at HPS Pharmacies.

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HPS Pharmacies Announces Inaugural Enterprise Agreement

> *HPS Pharmacies' pharmacist group were pleased with the final outcome produced with the implementation of the EA and look forward to the stability this will bring for HPS Pharmacists moving forward.*
>
> – Jonathan Soon, HPS – Coburg, Clinical Pharmacist, HPS Pharmacies

In April 2012, HPS Pharmacies embarked upon a consultative process to deliver the business a Pharmacy Manager, Pharmacist In-Charge and Pharmacist Enterprise Agreement (EA) to formally define their employment opportunities and conditions.

With the conclusion of successful negotiations between HPS Pharmacies, Professional Pharmacists Australia, and the employee bargaining representatives, the proposed EA was put out to vote, and it is with great pleasure that HPS Pharmacies announces the inaugural EA has been voted in and approved by HPS Pharmacies' pharmacist community with a resounding affirmative vote of 81.2%.

HPS Pharmacies employee and EA employee bargaining representative, Jonathan Soon, says "HPS Pharmacies' pharmacist group were pleased with the final outcome produced with the implementation of the EA and look forward to the stability this will bring for HPS' pharmacists moving forward."

"The negotiation process was very collaborative and HPS Pharmacies was responsive to our needs and listened to our requests and concerns," he says.

Whilst HPS Pharmacies' pharmacists have always enjoyed remuneration significantly higher than the Pharmacy Industry Award hourly rate, the newly introduced agreement will deliver to pharmacists:

- Wage increases, including annual CPI rises;
- Incorporation of Continuing Professional Development and tertiary study assistance arrangements;
- An established career pathway; and
- Recognition of specialist pharmacists and compensation.

Following several months of negotiations, and swift approval by Fair Work Australia to ensure all legislative requirements have been met, HPS Pharmacies was able to roll-out the EA to its pharmacist community.

Tracy Dickens, HPS Pharmacies' Human Resource Manager, says "this achievement is representative of a year's worth of effort, involving close collaboration between HPS Pharmacies and the bargaining representative committee to develop a robust Enterprise Agreement."

"We are excited to deliver certainty for HPS Pharmacies' pharmacists moving forward with this agreement now in place until 30 June 2015," says Tracy.

Tony Wyatt, HPS Pharmacies' Partner and Chief Executive Officer, says "I would like to take this opportunity to thank the bargaining representative committee, all HPS Pharmacies pharmacists, and especially the Operations and Human Resource teams for all their efforts in delivering this to the business."

"This project has been a key focus for the business over the past 12 months, and will provide a strong foundation for the future of HPS Pharmacies' pharmacists moving forward. HPS Pharmacies is proud of this fantastic outcome that will continue to successfully drive HPS Pharmacies into the future, as the employer of choice within the pharmacy industry," says Mr Wyatt.

From The Team

Dominic Coppola

Partner/Regional Operations Manager – SA/NT

HPS Pharmacies' position on Antimicrobial Stewardship (AMS) is unwavering, and is committed to achieving cost-effective, quality use of antibiotics and reducing the emergence of antimicrobial resistance within the population. HPS Pharmacies' clinical pharmacists are pivotal to the success of antimicrobial stewardship programs in hospitals, assisting with strategy implementation that encourages appropriate prescribing of antibiotics.

Our clinical pharmacists support AMS strategies by ensuring formulary restrictions and practice guidelines are followed, and by participating in activities that promote safe and prudent use of antibiotics. The responsibilities of HPS Pharmacies' pharmacists in antimicrobial stewardship include, but are not limited to; conducting Drug Use Evaluations (DUE's), providing referenced recommendations, policy development, and education of health professionals on antibiotic use and prescribing.

HPS Pharmacies' Antimicrobial Stewardship Program has been developed to support guideline-based prescribing. The program consists of a series of modules, designed to address antibiotic use in various clinical settings with the aim to improve patient outcomes, ensure cost effective therapy, reduce medication related adverse events, and reduce antibiotic resistance.

Clients who have adopted this program have experienced strong results. The program has had proven success in improving antimicrobial prescribing habits in numerous client settings, along with decreasing overall treatment costs and assisting clients in achieving relevant accreditation standards and expectations.

Angie Lawson

Systems Training Consultant

To assist HPS Pharmacies with the ongoing learning and development of its employees and clients, the Information Technology (IT) and Human Resources teams have introduced a hosted eLearning solution to the business.

This eLearning tool has been designed as a valuable resource internally, allowing HPS' existing employees to meet compliance obligations from a large library of courses, along with a customised HPS Pharmacies induction for new employees. Additional benefits to the business include reduction in the costs of; administration and facilitation of learning and development, time spent on identifying relevant and legislative content, travel costs for remote employees or facilitators, and the ability to provide consistent training to employees, including evidence for successful completion of associated assessments.

Additionally, eLearning will be rolled-out to clients in the future and will facilitate knowledge sharing, including the potential for remote training, along with an enhanced communication portal with those located in isolated areas. HPS Pharmacies will also utilise the eLearning solution throughout the implementation of new IT systems for a number of clients, ensuring clients receive consistent and professional training in a timely manner.

I am excited to be involved in the introduction of eLearning as HPS Pharmacies continues to deliver improved and innovative services to its clients and strives to be the employer of choice within the industry.

Alan Tuxford

Regional Operations Manager – VIC/TAS

As Regional Operations Manager, VIC/TAS, I'm responsible for directing, supporting and monitoring the delivery of services across a broad spectrum, including hospitals, cancer care, custodial care, and fertility services to name a few. I work closely with pharmacy managers and clients to ensure HPS meets the industry's evolving demands, whilst providing the best pharmaceutical care possible for patients.

Our continuous drive and determination to improve the quality and standard of pharmaceutical care has powered the development of our innovative Clinical Pharmacy Services tools. The tools have been designed to qualitatively and quantitatively define and determine the exact scope and extent of clinical services that will be provided in any healthcare setting.

HPS Pharmacies will be able to work collaboratively with our clients to target and customise clinical pharmacy services to the needs of each unique environment, including medication management plans, medication reconciliation, and medication history reviews.

Built on the strong foundation of best practice guidelines and professional standards, these tools have been entangled with the quality measures of ACHS and NSQHS accreditation standards. This deliberate design matrix will ensure confidence that the suite of HPS Pharmacies' cognitive services not only underpins the quality of pharmaceutical care to our patients, but will serve to support, document and exceed the accreditation needs of our clients.

Megan Farnsworth

Partner/Regional Operations Manager – QLD/NSW

HPS Pharmacies is privileged to be partnered with Healthscope for many years, and further strengthens its relationship with the build of a new on-site pharmacy in New South Wales.

In 2012, Sydney Southwest Private Hospital announced its intentions to open a new oncology unit to provide chemotherapy services to the south western community of Sydney, and HPS has been actively involved from the outset to bring these services to fruition.

Already a current client, with dispensing and clinical pharmacy services delivered off-site from HPS Pharmacies' Norwest site, HPS Pharmacies were eager to support Sydney Southwest Private Hospital in their new endeavour. To provide added support whilst the pharmacy was undergoing construction, HPS stationed a specialist oncology pharmacist, Anjana Rao, on-site for the unit's opening to provide this expertise. Anjana will continue to lead the HPS team in the delivery of oncology, dispensary and clinical pharmacy services as Pharmacy Manager of the new site.

The new pharmacy includes the provision of on-site chemotherapy manufacturing, and will provide realised benefit to the hospital, doctors and patients undergoing treatment at Sydney Southwest.

This is the first dedicated oncology compounding pharmacy for the business in NSW, and I am excited for this new development in expanding our national oncology services to the state of NSW.

Pharmacy Business

Healthcare Demographics Drive Reform

AHPRA (Australian Health Practitioner Regulation Agency) has begun publishing statistics of healthcare registrations which show that half of both the nursing and medical practitioner populations are distributed either side of 45 years of age. In particular, more than 10% of practicing medical practitioners are over 65, and may soon leave a serious hole in our healthcare system.

Pharmacists, however, are at the opposite end of their cycle, with the shortages of the '90s driving increased university intakes so that half the population are no older than 35. Women represent 90% of nurses and midwives, 40% of medical practitioners, and 60% of pharmacists.

The demographics of our various professions will impact on practitioner styles, management, and practice structures long into the future. Our increasingly ageing population demands an ever expanding healthcare system; which competes against other industries and other countries for its skilled labour, and is constrained in its capacity to increase training opportunities.

The *Council of Australian Governments* initiated the formation of AHPRA to improve flexibility in our health workforce; and of *Health Workforce Australia* to manage and oversee its reform. As well as improving supply of practitioners, reforms will include new models of care and redesigning of roles in multi-disciplinary healthcare teams.

An untrained observer can see that over the next decade, professional roles must be realigned to match the resources available, and the maturing crop of young pharmacists may find themselves taking on a wider range of responsibilities in response to need.

References:

1. Health Workforce Australia. Australia's Health Workforce Online. Adelaide, Australia. Available from <www.ahwo.gov.au>. Accessed 11 April 2013.
2. Australian Health Practitioner Regulation Agency. AHPRA. Melbourne, Australia. Available from <www.ahpra.gov.au>. Accessed 11 April 2013.
3. National Health Workforce Taskforce. Health Workforce in Australia and Factors for Current Shortages. KPMG; 2009.

Tribunal supports Di-Gesic® and Doloxene®

The Administrative Appeals Tribunal surprised many medical professionals by recommending the continued registration of dextropropoxyphene. Their reasons are interesting, starting from the observation that a medicine may lose registration if "it appears to the Secretary (of the Department of Health and Ageing) that the quality, safety or efficacy of the goods is unacceptable".

With no challenge to the quality, it remained for the Therapeutic Goods Administration (TGA) to prove the safety and efficacy to be unacceptable.

The tribunal found that Di-Gesic® and Doloxene® are effective, although not exceptionally so, and that their safety profile at therapeutic doses is similar to other weak opioids. The narrow therapeutic window means that there is an ongoing risk of toxicity or death from accidental, or intentional, overdose. They agreed with the TGA that suicide is not a valid reason to withdraw access to any drug from eligible patients, particularly as there are so many other drugs that a determined person could choose.

Dextropropoxyphene was found to be the only available option for patients who are unable to metabolise either codeine or tramadol. These patients, estimated at between 0.1% and 1% of the population, became pivotal as the withdrawal of registration would not support the preferred position that "if the interests of the few can be reconciled with the interests of the many, then they should be, rather than overridden."

Aspen and the TGA will now negotiate stringent controls on pharmacists and prescribers to confine supply to medically stable and fully informed patients that can't use other analgesics, and that are not at risk of overdose (accidental or intentional).

Reference:

1. Administrative Appeals Tribunal of Australia. Aspen Pharmacare Australia Pty Ltd and Minister for Health and Ageing, 2013. AATA 197.

Sustaining Chemotherapy Services

Concern over the safe provision and delivery of chemotherapy medicines to cancer sufferers following the impact of savings through *Price Disclosure*, has seen a recent senate enquiry recommend that the Department of Health and Ageing work with industry stakeholders to comprehensively review chemotherapy funding arrangements in order to "ensure the ongoing supply of these drugs across all services".

Medicare Australia PBS data shows that more than 13,000 life-saving infusions are prepared and dispensed by community and private hospital pharmacies for cancer patients each week.

While *Price Disclosure* has led to massive savings for the government after drug patents expire, it is now recognised that the associated margins had previously cross-subsidised the provision of many specialty services associated with supplying chemotherapy.

Catholic Health Australia voiced a common fear that continuing to ignore the complexity and cost of providing a full cancer service will mean that "over time, private hospitals will have no choice but to withdraw from the provision of some chemotherapy services", creating an impossible burden for public hospitals.

Without intervention, patients risk having access to chemotherapy services restricted, being forced to travel further for their treatments, and/or being forced onto potentially long waiting lists in the public health system, which is also affected by the funding model. This may in turn lead to worse outcomes for patients in the long term.

Any disruption to cancer care services, particularly in regional and rural areas, is considered unacceptable. There are more than 40 regional oncology clinics or hospitals considered to be 'at risk' due to this funding crisis. The Government must ensure these essential and highly toxic medicines can continue to be prepared, and delivered, safely to patients throughout Australia, without any additional costs to patients, pharmacists, cancer clinics or hospitals.

The senate enquiry focussed on patient access to treatment and the costs of preparation, delivery, and administration for pharmacists, suppliers, and hospitals, where this new review will thoroughly examine existing funding arrangements, and explore new models to achieve a sustainable structure that recognises and manages all the components of chemotherapy dispensing and supply, including the clinical services provided during treatment.

To this end, HPS Pharmacies welcomed the Government's acknowledgement of the need for reform, and importance of the private sector, demonstrated by investment in interim funding to ensure continuation of chemotherapy services during the review.

HPS Pharmacies continues to be active through the *Community Pharmacy Chemotherapy Services Group*, representing all providers of chemotherapy services to the private sector. The group's priority is "to place patients' interests, care and wellbeing first and foremost in the considerations of decision makers".

They will be keen to present to the review committee that three major concerns for patients continue to be:

- **Safety:** ensuring the safe provision of all medicines to patients.
- **Cost:** the cost to patients and their families of care, and the cost to advanced care pharmacists, private hospitals, and cancer clinics in providing chemotherapy safely to patients.
- **Access:** ensuring equitable and timely access to treatment locations in both private and public sectors and in particular, in regional and rural regions.

References:

1. Senate Committees. *Supply of chemotherapy drugs such as Docetaxel.* Canberra; Parliament of Australia; 2013. Available from <www.aph.gov.au/Parliamentary_Business/Committees/Senate_Committees?url=clac_ctte/chemotherapy_drugs/index.htm>. Accessed 8 April 2013.
2. Department of Health and Ageing. *PBS Chemotherapy Medicines Review*. Canberra: Department of Health and Ageing; 2013. Available from <www.health.gov.au/chemo-review>. Accessed 7 June 2013.

A World Without Antibiotics

Ly Ching Lam, Clinical Pharmacist
HPS – Norwest, New South Wales

It is difficult to imagine modern medicine without antibiotics. Chemotherapy, organ transplantation, and even basic surgical procedures would not be possible if it weren't for the use of antibiotics. It has been a mere 80 years since the serendipitous discovery of penicillin in 1929, and its first application in the 1940s, but we are now faced with a grim but very real possibility of reverting to the conditions of a pre-antibiotic era.

Bacteria are champions of evolution. They existed long before homo sapiens did, and will continue to persist long after we are gone. They can survive in extreme conditions, reproduce asexually within minutes, and are adapting at a rate which far exceeds that with which we are able to discover and synthesise new antibiotics. This bleak situation has been borne from decades of widespread antibiotic misuse.

The clinical applications of penicillins were quickly limited by the ß-lactamases, enzymes that cleave the ß-lactam bond rendering the antibiotic ineffective. The scientific and medical community responded with the discovery of cephalosporins and carbapenems. The most prevalent Gram-negative pathogens, such as *Escherichia coli*, *Salmonella enterica*, and *Klebsiella pneumoniae*, are responsible for many common community-acquired infections, but a strong correlation between antibiotic use in the treatment of these diseases and antibiotic resistance development has been observed over the past half-century.

As 3rd generation cephalosporins are no longer able to be used as empirical therapy in many countries, carbapenems have represented the last line of defense against Gram-negative bacilli.

Until the 2000s, carbapenems were almost uniformly active against resistant Gram-negative organisms, but new mechanisms of resistance have now emerged. They include changes to the cell membrane 'porins' that block the entry of the antibiotic, or via 'efflux pumps' that cause the antibiotic to be effectively pumped out of the bacterial cell.

Mycobacterium tuberculosis is the archetypical human pathogen; it evolved with the human race and currently infects as much as one third of the world population. While the ground-breaking discoveries of streptomycin and isoniazid provided vital treatments, resistance development was rapid.

The introduction of cocktails of anti-tuberculosis drugs has become an essential treatment regimen, with considerable success; however, multidrug resistance continues to compromise therapy throughout the world. *M. tuberculosis* strains resistant to four or more of the front-line treatments (i.e. extremely drug-resistant [XDR] strains) have appeared and spread rapidly in the last decade or so. And now there are TDR strains, which are 'totally drug-resistant'.

Among the Gram–positive organisms, methicillin resistant *Staphylococcus aureus* (MRSA) represents a great therapeutic challenge. MRSA appeared within just three years of the introduction of methicillin in 1959 and inexorably lead to multi-antibiotic resistant variants. The acronym now denotes multidrug-resistant *S. aureus*. Some MRSA strains have shown a disturbing trend in resistance to glycopeptides and even more recently introduced agents, such as daptomycin and the oxazolidinones.

Concerning hospital-acquired diseases, *Pseudomonas aeruginosa* has evolved from being an infection of burn wounds into a major nosocomial threat. Again in this case, antibiotic resistance mechanisms evolved coincidentally with the introduction of new antibiotic derivatives, compromising the most effective treatments (such as the ß-lactams and aminoglycosides).

Currently, the clinical frequency of antibacterial resistance in Australia to *P. aeruginosa* with amoxicillin, macrolides, clindamycin, tetracycline and most cephalosporins is 100%, and 15-30% with gentamicin, ciprofloxacin and norfloxacin. *P. aeruginosa* is of considerable concern for patients with cystic fibrosis; the pathogen is highly persistent and can avoid human immune defenses. Resistance development is associated with the lengthy antibiotic treatments of cystic fibrosis patients.

Perhaps the greatest cause for global concern is the novel enzyme – the New Delhi metallo ß-lactamase-1 (NDM-1), a growing but insufficiently publicised pandemic. It was first reported in 2009 in a Swedish patient who travelled to New Delhi and acquired a urinary tract infection due to a carbapenem-resistant *K. pneumoniae* strain.

This strain was resistant to every antimicrobial tested with the exception of colistin. The NDM-1 encoding gene is located on bacterial plasmids, which are easily transferable and capable of wide rearrangement, suggesting widespread transmission and plasticity among bacterial populations.

What is most disconcerting is that transfer may occur amongst unrelated bacterial isolates via horizontal gene transfer. NDM-1 has been isolated widely in enterobacteriaceae species including *K. pneumoniae*, *E. coli*, *E. cloacae*, *Proteus* spp., *Citrobacter freundii*, *K. oxytoca*, *M. morganii* and *Providencia* spp.

Most isolates remain susceptible to colistin and tigecycline, except those *Enterobacteriaceae* endowed with a natural resistance to these compounds such as *M. morganii*, *Proteus* spp. and *Providencia* spp. Presently, there have been at least 150 cases in India and Pakistan, 70 in the United Kingdom and several cases arising globally including Canada, Australia, Asia, Europe and the United States, illustrating widespread dissemination.

Concern about antimicrobial resistance in bacteria is not new. Numerous articles were published half a century ago highlighting this fact. Some action has been taken in response to the threat. Few countries have had the foresight to implement more stringent policies to mitigate the spread of resistance through Antibiotic Stewardship programs.

The *Infectious Diseases Society of America*, *US Centers for Disease Control and Prevention* (CDC), *European Commission*, and *European Center for Disease Prevention and Control* (ECDC) have campaigned to raise awareness and provoke the desperately needed action from governments and the pharmaceutical industry.

The reality is that the net commercial value of antibiotics is low and so antibiotic research is not a high priority for pharmaceutical companies. Among the proposals to overcome this barrier are orphan drug benefits, government incentives toward research and development, prolonged patents and expedited approval. Proposals and pronouncements lack the result that may only come from action.

So in the meantime, we have only the option of revisiting treatments that are more than 30 years old – antibiotics with unfavorable toxicity profiles and limited pharmacodynamic guidance while we wait for new antibiotics to emerge from the pipeline, and sense a pervasive belief in the scientific community that increasing antibiotic resistance is the new norm – an extremely costly attitude.

In 2000, the World Health Organisation produced comprehensive recommendations for curbing antibiotic resistance. These recommendations include national surveillance programs, rigorous infection control policies, banning of non-prescribed antibiotics, prudent antibiotic usage in hospitals and increased international collaboration. Unfortunately, many countries have failed to adopt such methods.

As long as people are able to purchase antibiotics without prescriptions, which is largely the case in many developing countries, and as long as prescribers continue to issue antibiotic prescriptions to treat viral infections, we will continue to see the treasury of antibiotics, which has served modern medicine so well, be stripped of its value.

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Clinical Article

From Compliance to Adherence to Concordance: The Evolution from Paternalistic Medicine to Patient Empowerment

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Correct use of medicine is a crucial factor in effective patient self-care and hence positive outcomes in any chronic disease. Different concepts have evolved from the notion of correct use of medicine, such as compliance, adherence and concordance.

Compliance is defined as "the extent to which the patient follows the health professionals' advice and takes the treatment". This concept is being replaced by the term 'adherence', as compliance may imply a submissive, uninvolved patient in a paternalistic setting.

Adherence is defined as "…the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider".

Concordance is a new concept which has evolved and is defined as "agreement between the patient and healthcare professional, reached after negotiation that respects the beliefs and wishes of the patient in determining whether, when and how their medicine is taken, and (in which) the privacy of the patient's decision (is recognised)".

For the purposes of this article, the term 'adherence' will be used to discuss contributing factors and influences in medicine-taking behaviour, consequences of poor adherence, and strategies to improve medicine adherence, thereby demonstrating the shift towards the concept of concordance.

The literature shows that adherence is a complicated notion, the culmination of the interaction of a variety of aspects such as the features of the condition, social background, access, and patient beliefs and characteristics. Factors that can influence adherence to medicines include gender, age, ethnicity, education, social support, marital status, mood impairment or cognition, number of prescribing doctors, and visiting more than one pharmacy; and it has been found that patients with a higher income and lower medicine expenses tend to be more adherent.

There are several reasons cited for patients not adhering, such as;

- Forgetting to take the medicine
- Affordability
- Concern about safety or effectiveness
- Fear of or experiencing adverse effects
- Confusion over the directions
- No longer feeling unwell or not feeling any different
- Feeling that they cannot manage with the number of medicines they should take and how to coordinate them
- Having dexterity challenges, or
- Simply being too unwell.

Adherence to medicines is a variable aspect of treatment, as daily influences impact upon everyday choices, and chronic illnesses involve symptoms, exacerbations, and future impacts, each of which are frequently changing. In a study by Elliott et al (2007) the team concluded that continuing communication with patients about their medicines is necessary, and requires collaboration across disciplines for patients with chronic conditions. In order to positively guide patient decision-making regarding medicine use, health professionals need to be informed of the patients' current as well as previous choices, as they may place importance on different issues from the prescribers; and with each newly introduced drug the new decisions made by the patient may not always be shared with the prescriber. Hence, when new medicines are initiated, good practice would indicate that a health professional is available to discuss medicines with patients.

Adherence is an important area to consider, as patients are generally poorly adherent to medicines, particularly in chronic disease states. Lack of adherence can lead to medicine wastage, morbidity

and hospitalisation. Rates of adherence for a number of chronic medicine regimens have been found to be between 40-50%, and non-adherence is linked to more frequent doctor consultations, and increased rates or duration of hospitalisation. Medicine non-adherence is reported in the literature at a rate of approximately 50% in developed nations, with around half of this proportion being deliberate and the remainder due to ignorance of not taking medicine as they should or due to a complicated regimen.

In a study by Lewis (1997), it was found that sickness due to non-adherence to medicines in the United States costs approximately US$100 billion per year. The National Audit Office reported that returned medicines in England for 2007 approximate to £100 million annually. Noens et al (2009) found that significantly more chronic myeloid leukaemia (CML) patients with an unsatisfactory response had not taken their imatinib (23.2%) compared to those who achieved peak response (7.3% imatinib not taken). In addition, the team found there were significantly fewer missed tablets (9%) in patients who demonstrated a complete cytogenic response, in comparison to the 26% with an incomplete cytogenic response, in a patient group who underwent treatment for a minimum of 12 months with imatinib.

The fact that a disease may possibly be life-threatening does not appear to increase medicine adherence, and findings indicate that adherence can decrease over time. A study by von Mehren and Widmer (2011) found that the population of patients who adhered to imatinib for CML and gastrointestinal stromal tumours decreased from almost 100% during the first four months of treatment to 23% at the fourteenth month. It was also reported that nearly 30% of patients ceased their imatinib for 30 or more days during year one of treatment for CML or gastrointestinal stromal tumours. In another study conducted by Partridge et al (2003), it was shown that long-term adherence to tamoxifen reduced from 83% in the first year of treatment to 50% when the fourth year milestone was reached.

Encouraging open and equal discussion about medicines between both the health professional and the patient leads to improved prescribing practices and better patient adherence. Many studies demonstrate the intervention of a pharmacist enhances medicine adherence rates. Carter et al (2005) report that support networks, the active participation of patients, and advocating self-care are significant contributors to positive treatment outcomes.

Furthermore, patients report an enhanced quality of life when they are contented with the level of information regarding their medicines that is provided to them, and Cassileth et al (1980) similarly mention that patient mechanisms for managing can be derived from the information pharmacists provide.

Concordance refers to a consultative procedure where a collaborative approach between doctor and patient leads to prescribing. Pharmacists can have a role in facilitating this process, thereby alleviating the doctor to focus on diagnosis and formulating a treatment plan. The concordance approach can lead to a more empowered patient as their feelings have been discussed and respected, an open forum encouraged to discuss any ensuing treatment challenges, and hence there is a greater likelihood of the patient following the prescribed treatment and therefore commit to a more transparent decision-making process within which they have played a role.

The philosophy is founded upon delivery of information and viewpoints on the part of the prescriber, and in valuing patient autonomy in reaching decisions rather than imposing directions upon them without further discussion.

Optimising patient outcomes from taking medicine is a multi-faceted concept which relies on the interplay of many ever-changing factors. Ultimately, medicine adherence is founded in an open and trusting relationship between the patient and members of the healthcare team, and the establishment of a positive rapport to foster a team approach involving the patient at the centre.

In order to establish a sincere collaboration, and then a mindfulness of, a pledge to respecting patient autonomy and exercising competent communication skills is required to facilitate the interaction. Greater success in achieving patient adherence may occur by eliciting patient opinions, truly listening to them and assisting them to rationalise difficulties in order to complete the decision-making process, compared to simply dictating how patients should proceed.

References for this article can be found in the online version published in the HPS Pharmacies Knowledge Centre.

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Can I Crush It?

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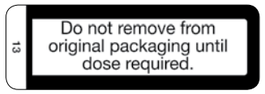

Figure 1. Cautionary Advisory Label Number 13

Ideally, oral dose forms of medicines such as tablets and capsules should be administered in their original, unaltered state. However many people, particularly older patients and children, may find it difficult to swallow them. In some cases patients are unable to take medication orally at all, requiring administration via an enteral feeding tube.

Altering solid dosage forms by crushing or splitting tablets, or by opening capsules, is a tempting and practical option, but not always an appropriate one. Problems may include;

- Loss of efficacy
- Increased risk of toxicity
- Taste and texture issues
- Reduction in stability, and
- Work Health and Safety (WHS) concerns.

In the event of an adverse clinical outcome, there may also be legal implications for health professionals involved in altering a commercial product contrary to the manufacturer's product licence.

The excellent new reference *Australian Don't Rush to Crush Handbook* is an invaluable guide to the options available for people unable to swallow oral medications.

Assessment of swallowing ability

A person's ability to swallow food and orally administered medicines can be affected by;

- **Physical difficulties** – dysphagia (secondary to stroke, Parkinson's disease, multiple sclerosis, Motor Neurone Disease [MND], reduced level of consciousness, dry mouth).
- **Physiological factors** – deteriorating cognition (e.g. dementia), inability or aversion to swallowing tablets.

Dysphagia can be a particular problem in older people, due to weakening of the muscles involved in swallowing, a reduction in salivary gland function, and the increased likelihood that they will have developed a medical condition affecting the swallowing process.

Review by a speech pathologist should be considered in both the hospital and aged care setting for assessment of chewing and swallowing. If the inability to swallow relates to a particular time of the day, just changing medicine administration times may be all that is needed to resolve the problem.

Review of the medication regimen

A patient's recently developed swallowing problem should be seen as a good opportunity to completely review their medication regimen, with a view to finding suitable alternative formulations such as liquids, powders for suspension, patches, or suppositories.

If these are not an option, it may become necessary to consider alternative drugs, or cease some medication altogether.

If dry mouth (xerostomia) is a contributory factor, identify any possible drug related causes such as antihistamines, tricyclics antidepressants, selective serotonin reuptake inhibitors, tiotropium/ipratropium, oxybutynin, and opioids. Consider the possibility of ceasing any medications at this stage, or using a suitable alternative tablet formulation, patch, or liquid.

Consider the following options;

- **An alternate drug in the same class** may have a prolonged duration of action, but still be an immediate release formulation that can be crushed, e.g. amlodipine in place of felodipine SR.
- **An alternate form of the same drug** may be suitable to crush or be otherwise modified to enable administration, e.g. isosorbide dinitrate instead of mononitrate SR, or morphine sulphate as Kapanol® instead of MS Contin®. There may also be a chewable or soluble form available, e.g. sodium valproate chewable tablets.
- **A liquid if available,** e.g. sodium valproate (Epilim® Syrup), phenytoin (Dilantin Paediatric®), or oxycodone (OxyNorm® Liquid). It may be necessary to adjust the dose, or dosing interval, to achieve the same effect. Monitor closely.
- **A soluble tablet.** This may be an option, e.g. soluble paracetamol, but needs to be discussed with a pharmacist as many soluble tablets are high in sodium content and may be inappropriate for some medical conditions such as hypertension.

Alteration of an oral formulation

If there are no suitable alternatives available commercially, then it may be necessary to consider crushing, or otherwise modifying, the existing dosage form.

In many cases, this is quite acceptable, but it is still important to consider the risks, including;

- Reduced effectiveness of the medication
- Increased risk of toxicity
- Possible risks to healthcare workers or carers preparing the medication
- Making the drug so unpalatable that adherence is reduced, and
- Reducing the stability of the drug.

A pharmacist should be consulted for advice before crushing is initiated, and the product information should be checked carefully. Consult specialised texts, if available (see references). Pharmacists may need to contact the manufacturer directly.

Categories of medications which should not be altered

Understanding the reason, and method of treatment of tablets and capsules helps us to know when and why they should only be swallowed whole.

Altered absorption or release

Many of these products can be identified by postscripts to the product name such as CR, MR, XR, XL, CD, or SR which implies a treatment to modify the rate of release of the medication, such as 'CR' meaning *Controlled Release*. They are designed to release the medicine over an extended period (12-24 hours). Crushing can result in a large bolus dose, high peaks, and toxicity. For example crushing verapamil SR tablets increases the risk of hypotension and bradycardia, whereas Kapanol® or MS Mono® capsules may be opened if the pellets are swallowed without chewing to prevent high plasma peaks and the risk of opioid toxicity, alternating with long periods of inadequate analgesia between doses.

Enteric coatings cover the whole tablet, or the pellets within a capsule, to protect the medicine from gastric acidity, and allow dissolution in the intestine. It improves bioavailability of medicines that are unstable in an acid environment, such as omeprazole, or reduce gastrointestinal side effects as with non steroidal anti-inflammatories.

Altered stability

Film coating on tablets protects the contents from atmospheric light and moisture, which may cause them to break down rapidly. Nifedipine, for example, is very light sensitive, where aspirin is hygroscopic. Do not remove non-enteric coated tablets from packaging until immediately before use, as described on the 'Cautionary Advisory Label' (Figure 1) applied to the packaging.

Failure to reach site of action

Enteric coatings can also control the specific site of release of medicines within the gastrointestinal tract. Crushing can result in loss of efficacy and/or increase of side effects. Mesalazine, for example, is intended to act in the lower small intestine or colon, depending on the brand. Crushing can increase the risk of kidney damage and reduce efficacy.

Local irritant effect

Some coatings are to protect the oesophagus and stomach from a directly irritant effect of the medicine, as seen with bisphosphonates and tetracyclines. The bisphosphonate (alendronate) can cause severe upper gastrointestinal irritation and/or ulceration. If tablets must be crushed, ensure plenty of water is taken to wash away the particles.

Work Health and Safety

Highly potent and toxic medicines including cytotoxics, teratogens, contact irritants, and hormones can be dangerous to the handler. Finely crushed particles may be inhaled, so specific safety precautions should be followed to minimise risks.

Finasteride presents a risk to male foetuses (Australian category X). Pregnant women, or women of child-bearing age, should not handle crushed or broken tablets. Cyclophosphamide and methotrexate (which may also be used for arthritis) are cytotoxic. Isotretinoin is used to treat acne, but is teratogenic; and chlorpromazine is an irritant which causes contact dermatitis.

Palatability

Drugs like ibuprofen and quinine have an unpleasant taste, whereas hydroxychloroquine is extremely bitter. Sugar coatings or film coatings may be used to mask the taste or smell of the medicine. While crushing will not change the medicinal benefit, the patient may become distressed by the experience.

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Drugs, Prolonged QT Interval and Torsades de Pointes

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The QT interval of an ECG (electrocardiogram) represents ventricular depolarisation and repolarisation. It is normally less than 440 milliseconds (although this may vary between individuals and by gender).

Torsades de Pointes (TdP) is a form of polymorphic ventricular tachycardia that occurs in patients who have a long QT interval when in normal rhythm (usually sinus rhythm, but sometimes in patients with atrial fibrillation). Prolongation of the QT interval can predispose individuals to this potentially lethal arrhythmia (and less commonly, other arrhythmias) by prolonging repolarisation, which induces early afterdepolarisations and spatial dispersion of refractoriness. The risk of TdP is increased when the QT interval is above 500 milliseconds or increased from the patient's baseline by at least 60 milliseconds.

Prolongation of the QT interval can be caused by many factors including:

- Congenital long QT syndrome (genetic; generally autosomal dominant disorders)
- Pre-existing cardiac structural disease (such as heart failure and myocardial infarction)
- Bradycardia
- "Stimulant conditions" such as exercise or emotion
- Electrolyte abnormalities (hypokalaemia, hypomagnesaemia and hypocalcaemia)
- Testosterone suppression
- Thyroid disease
- Female gender
- Increasing age, and
- Drugs.

The highest risk population appears to be females between menarche and menopause.

Prolongation of the QT interval is quite often asymptomatic and self-limiting but can recur if underlying causes are not corrected. TdP produces no effective cardiac output, therefore if an episode is less than 10 seconds a patient may not notice it, however longer than this may cause a collapse, potentially with loss of consciousness. Seizures may occur due to brain hypoxia. Death may occur if the abnormal rhythm is not terminated within a few minutes, however if it does terminate, the patient will recover consciousness quickly.

Treatment for TdP is slow intravenous injection of magnesium sulphate as well as a drug to shorten the QT interval such as isoprenaline. Electrolyte abnormalities should be corrected and any drugs prolonging the QT interval should be stopped.

Drugs generally lengthen the QT interval via interacting with some of the cardiac membrane ion channels, particularly the potassium channel. The identification of a prolonged QT interval is difficult. It is important to manually measure the interval and not rely on the generated measurement on the ECG, and measure this on a QT nomogram. QRS widening on the ECG may cause prolonged QT, however this is not a risk for TdP (such as in bupropion poisoning).

Drugs that prolong the QT interval are separated into three categories of risk for producing TdP, and quality and quantity of evidence supporting the conclusion:

1. Proven risk of TdP when given therapeutically

Substantial evidence supports the conclusion that these drugs prolong the QT interval and have a risk of TdP when used in therapeutic doses.

- **Antiarrhythmics:** Amiodarone, Disopyramide, Flecainide and Sotalol;
- **Antidepressants:** Citalopram and Escitalopram;
- **Anti-infectives:** Azithromycin, Chloroquine, Clarithromycin, Erythromycin, Moxifloxacin and Pentamidine;
- **Antipsychotics:** Chlorpromazine, Droperidol and Haloperidol;
- **Gastrointestinal agents:** Cisapride and Domperidone; and
- **Miscellaneous:** Arsenic Trioxide, Dextropropoxyphene, Methadone and Sevoflurane.

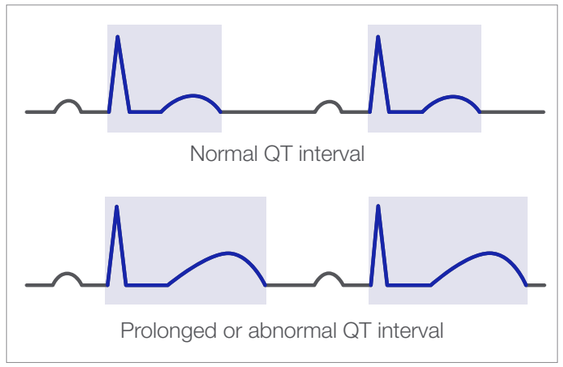

Figure 1. Schematic representation of ECG trace

2. Drugs with conditional risk of TdP

Substantial evidence supports the conclusion that these drugs prolong the QT interval and have a risk of TdP under certain known conditions (e.g. not in therapeutic doses under such conditions as drug interactions or excessive dosing).

- **Antidepressants:** Fluoxetine, Tricyclic antidepressants, Paroxetine*, Sertraline* (*lower risk than Tricyclic antidepressants);
- **Anti-infectives:** Ciprofloxacin, Co-Trimoxazole, Fluconazole, Itraconazole, Ketoconazole, Mefloquine and Ritonavir;
- **Antipsychotics:** Amisulpride; and
- **Miscellaneous:** Cocaine, Diphenhydramine, Galantamine, Loratadine, Pazopanib, Propranolol, Sevoflurane, Solifenacin and Toremifene.

3. Drugs with possible risk of TdP

Substantial evidence supports the conclusion that these drugs prolong the QT interval but insufficient evidence that they cause TdP.

- **Antidepressants:** Moclobemide and Venlafaxine;
- **Anti-infectives:** Atazanavir, Foscarnet and Voriconazole;
- **Antipsychotics:** Clozapine, Paliperidone, Olanzapine, Quetiapine, Risperidone, Sertindole and Ziprasidone;
- **Gastrointestinal agents:** Dolasetron, Famotidine, Granisetron and Ondansetron; and
- **Miscellaneous:** Alfuzosin, Amantadine, Dasatinib, Fingolimod, Indapamide, Lapatinib, Lithium, Nilotinib, Roxithromycin, Sorafenib, Sunitinib, Tacrolimus, Tamoxifen and Vardenafil.

The degree of QT prolongation associated with drug use appears to be related to drug plasma concentration which is affected by dose, frequency, route of administration, and variables that interfere with the pharmacokinetics of the drug.

Therefore, to reduce the risk of TdP in a patient with risk factors for prolonged QT:

- Avoid drugs that prolong QT. If this will reduce treatment efficacy, use a drug which is less likely to cause TdP (i.e. one that has little evidence of TdP or needs certain conditions to prolong QT);
- Use the lowest possible dose;
- Use the oral route where possible;
- If given intravenously, give as slowly and as diluted as possible; and
- Reduce pharmacokinetic and pharmacodynamic interactions by avoiding the concomitant use of agents which may prolong the QT interval, drugs that will inhibit the metabolism of drugs that prolong QT interval (i.e. cytochrome P450 inhibitors), or drugs that increase the concentration of these agents.

For example, in a patient with severe community-acquired pneumonia who requires intravenous administration of azithromycin, along with other antibiotics, whilst sputum and blood cultures are pending. Administration of azithromycin in 500mL over three hours is preferable to the more routine administration of 250mL administered over one hour (unless the patient is fluid restricted). If the patient is nauseous, metoclopramide should be used over domperidone.

Although the frequency of TdP is low, it can occur as often as 2-3% with some drugs, and can be fatal. Practical measures can be taken to prevent it by understanding risk factors and negotiating therapy to still provide the best patient outcomes.

References for this article can be found in the online version published in the HPS Pharmacies Knowledge Centre.

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Perioperative Anticoagulation

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In this article perioperative anticoagulation refers to balancing the risk of bleeding and the risk of a blood clot in patients taking anticoagulants who undergo elective surgery. Management will depend on:

- The medication prescribed to prevent thrombosis;
- The risk of thrombosis; and
- The risk of bleeding from the surgery.

Warfarin

Warfarin is often regarded as the most challenging antithrombotic agent to manage perioperatively, primarily due to its long half-life. The *Australasian Society of Thrombosis and Haemostasis* released a consensus statement on the subject, which gives some guidance in management. The first aspect in need of consideration is the risk of bleeding from surgery. If the risk is low (e.g. minor dental surgery or minor dermatological procedures), warfarin can be continued without disruption.

If the risk of bleeding from surgery is high, warfarin therapy will need to be interrupted, and the risk of thrombosis, while the patient is not taking warfarin, needs to be considered. After cessation of warfarin, it takes a significant amount of time for the INR (International Normalised Ratio – a measure of how long it takes the blood to clot) to fall to a level at which it is acceptable to perform surgery. During this time the INR is not in the therapeutic range, putting the patient at an increased risk of thrombosis.

The patient may require 'bridging therapy' with a shorter acting anticoagulant in the days before surgery which can be stopped suddenly to cover the patient during this period. This shorter acting anticoagulant may also be required in the days after surgery until the patient's INR returns to a therapeutic level. There is much disagreement among health professionals regarding which patients should receive bridging therapy. This decision is generally based on the patient's baseline risk of thrombosis.

If the patient has a low baseline risk of thrombosis, stopping warfarin 3-5 days before surgery will usually be sufficient time for the INR to fall low enough for surgery to be performed, and in these circumstances anticoagulant therapy during this time is generally not required. However, if the patient has a high risk of thrombosis, bridging is recommended. A shorter acting agent should be started 2-3 days before surgery, or when the INR is no longer therapeutic.

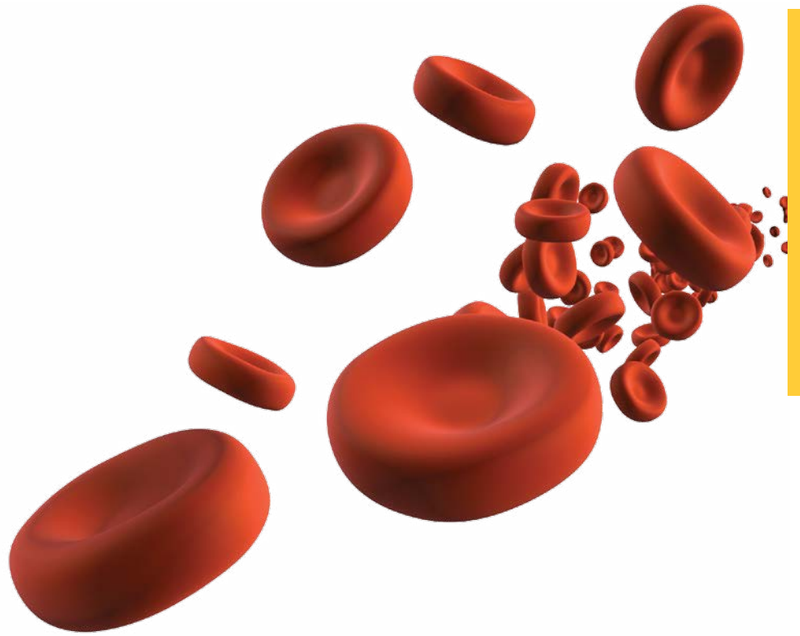
The agents of choice are unfractionated heparin, or low molecular weight heparin (e.g. enoxaparin). Heparin should be stopped 4-6 hours before surgery, while enoxaparin should be stopped 12-24 hours before surgery. Patients will also need thromboprophylaxis after surgery as per usual practice. The decision of which patients are classed as 'low' or 'high' baseline risk of thrombosis and therefore which patients should receive bridging therapy, is at the discretion of each physician, and varies markedly between prescribers.

Further information on the perioperative management of warfarin can be found on the *Medical Journal of Australia* website under "Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis".

Newer Oral Anticoagulants

This issue will occur less frequently with the introduction of the newer anticoagulants rivaroxaban (Xarelto®) and dabigatran (Pradaxa®), which are now sometimes used where warfarin was once the only option. Both these agents have a much shorter half-life than warfarin, which makes perioperative management easier. However, as they are new, there is limited data on the subject.

Dabigatran has a half-life of approximately 12-17 hours. In patients with normal renal function, the product information suggests dabigatran should be stopped at least 24 hours before standard invasive procedures. However, in cases where the patient is likely to be at a higher risk of bleeding (e.g. major surgery), or when there is delayed clearance due to renal impairment, stopping dabigatran up to 2-4 days before surgery should be considered.



Rivaroxaban has a half-life of approximately 5-13 hours, with younger patients generally having a shorter half-life (5-9 hours) and the elderly longer (11-13 hours). The product information suggests that rivaroxaban should be stopped at least 24 hours prior to surgery if possible.

However individual patient factors should be taken into account and the benefit or risk assessment may indicate rivaroxaban should be stopped even earlier, particularly where the patient is at very high risk of bleeding, or in major surgery where complete haemostasis is required.

Most people taking dabigatran and rivaroxaban will not require bridging therapy before surgery. The expert opinion is that provided the patient is of normal renal function and low bleeding risk these anticoagulants can be safely stopped for surgery for up to 48 hours. A minority of patients with special circumstances (e.g. renal impairment), may require bridging before surgery.

After surgery however, bridging is not required as both dabigatran and rivaroxaban have an immediate onset of action, and can be given at the time when heparin would normally be given.

For patients on warfarin, the INR is commonly used before surgery to check that warfarin has been cleared from the body. However, the INR result does not have an established correlation to the anticoagulative ability, or lack thereof, of either rivaroxaban or dabigatran. Therefore INR should not be used to determine a patient's bleeding risk, and hence suitability for surgery, if the patient has been taking either of those newer medications.

Another factor to consider is the reversibility of anticoagulation. The effect of warfarin can be reversed using vitamin K, however there is currently no product available which can reverse the pharmacodynamic effect of either rivaroxaban or dabigatran. Prothrombin complex concentrate (Prothrombinex™-HT), recombinant blood factor VII (NovoSeven® RT) and fresh frozen plasma have been used for immediate symptomatic management of clinically significant bleeding.

However, while non-clinical experimental studies have shown that prothrombin complex concentrate and factor VII reduce the anticoagulation effect of rivaroxaban and dabigatran, there is currently no data to confirm this effect in patients.

Conclusion

If interruption of anticoagulant therapy is required for surgery, this should always be done in conjunction with the medical practitioner who instigated the therapy. There are limited guidelines for the management of perioperative anticoagulation regarding warfarin and the newer drugs, dabigatran and rivaroxaban. If warfarin is stopped for surgery, bridging therapy with a short acting anticoagulant may be required.

While the newer drugs have shorter half-lives compared to warfarin, management is complicated by the lack of evidence regarding how long before surgery they should be ceased, and also inability to reverse their anticoagulant effect.

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Drugs Used in Cardiac Failure

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Chronic heart failure (CHF) is a condition that affects 1.5-2% of Australians, where the heart is unable to maintain a strong enough blood flow and is characterised by an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricles of the heart to fill with, or eject, blood. Shortness of breath on exertion is one of the most common symptoms, which may also include fluid retention, paroxysmal nocturnal dyspnoea, palpitations, syncope, orthopnoea, dry irritating cough and fatigue.

Risk factors for CHF include;

Common

- Coronary heart disease and prior myocardial infarction
- Hypertension, and
- Diabetes.

Less common causes

- Non-ischaemic idiopathic dilated cardiomyopathy (familial).

Uncommon causes

- Valvular heart disease
- Non-ishcaemic dilated cardiomyopathy (due to long term alcohol abuse)
- Chronic arrhythmia
- Drug-induced cardiomyopathy (particularly with chemotherapy drugs such as doxorubicin, daunorubicin, cyclophosphamide, paclitaxel and mitoxantrone), and
- Hypertrophic cardiomyopathy (familial).

Physical examinations are important for initial diagnosis, however clinical symptoms are often unreliable, and it is important to perform additional investigations as confirmation. As a minimum, investigations include electrocardiogram (ECG), chest x-ray, echocardiogram and blood tests.

Non-pharmacological management may be as important as prescribing appropriate medications. Regular physical activity has been shown to reduce physical deconditioning and help improve functional capacity and symptoms. Reduction of sodium intake is recommended to prevent fluid overload. Fluid management is a key measure in symptom monitoring and control for many patients. Alcohol is a direct myocardial toxin and may impair cardiac contractility. Smoking cessation is important as tobacco smoke is atherogenic, reduces the oxygen content in blood as well as provoking vasoconstriction.

There is increasing evidence to support use of combination pharmacological therapy to improve prognosis and control signs and symptoms. It is important to start with low doses and then gradually up-titrate to the optimal dose over several months. If symptomatic hypotension develops on combination therapy, the dose of angiotensin converting enzyme inhibitor (ACEI) and diuretic should be reduced before reducing the dose of beta blocker.

Angiotensin Converting Enzyme Inhibitor

Because of the major importance of activation of the renin-angiotensin-aldosterone system in CHF progression, the use of ACEIs in blocking this pathway is seen as a cornerstone of successful therapy. ACEIs have been shown to improve symptoms, reduce the risk of CHF-related hospitalisation and prolong survival.

ACEIs are first-line treatment for all classes of CHF, where therapy should begin with a low dose, then up-titrate slowly.

Common adverse effects: Hypotension, dizziness, hyperkalaemia, cough, renal impairment, angioedema (rare).

Angiotensin II Receptor Blockers (ARB)

Patients unable to tolerate ACEIs due to side effects such as cough or skin rashes, should be offered an ARB. Studies comparing the use of ACEIs and ARBs in CHF show similar outcomes.

If a patient had angioedema whilst on an ACEI, there is possible cross-reactivity and a harm-benefit analysis is required prior to initiating therapy.

Common adverse effects: Dizziness, hypotension, hyperkalaemia.

Beta Blockers

Beta blockers inhibit the effects of chronic activation of the sympathetic nervous system acting on the myocardium.

Bisoprolol, carvedilol and metoprolol succinate improve symptom control, prolong survival, reduce hospitalisations and mortality. Nebivilol is approved for use in the treatment of stable heart failure in patients above 70 years old.

Beta blockers are recommended for all CHF patients (including older patients and patients with peripheral vascular disease [without critical limb ischaemia], diabetes and chronic obstructive airway disease). Those on a beta blocker for other comorbidities (i.e. angina, hypertension) should be switched to a heart failure specific beta blocker.

Beta blockers may aggravate heart failure and cause symptomatic hypotension during initiation of therapy. These effects can be minimised by beginning at a low dose, and slowly titrating up. They should not be initiated during acute decompensation, but after the patient has stabilised.

Common adverse effects: Bradycardia, hypotension, dizziness, bronchospasm, cold extremities, insomnia, nightmares.

Diuretics

Diuretics increase urine sodium excretion and reduce fluid retention, providing rapid symptom improvement. Loop diuretics are the diuretics of choice in CHF, although they are commonly used with thiazide diuretics in clinical practice.

Chronic diuretic therapy has not been shown to improve survival and should only be reserved for symptom control.

Common adverse effects: Hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, hyperuricaemia, gout, dizziness, orthostatic hypotension, syncope.

Aldosterone Antagonists

Aldosterone receptors within the heart can mediate fibrosis and hypertrophy, and blocking them with aldosterone antagonists may provide benefit.

When added to existing treatment, eplerenone and spironolactone have been shown to improve symptoms and reduce the risk of death.

Aldosterone antagonists increase the risk of hyperkalaemia, particularly in the presence of ACEI/ARB and/or renal impairment. Spironolactone is also an androgen receptor antagonist, and may cause feminisation side effects.

Common adverse effects: Hyperkalaemia, hyponatraemia (spironolactone), hypotension, dizziness, endocrine effects (spironolactone) – gynaecomastia, menstrual abnormalities, sexual dysfunction.

Digoxin

The cardiac glycoside, digoxin, inhibits sodium-potassium adenosine triphosphatase, to improve inotropic responsiveness in CHF patients.

Digoxin has been shown to reduce CHF-related hospitalisations but not mortality.

Digoxin may be considered in patients with sinus rhythm who have not responded to the first-line therapies above, and also in patients who have atrial fibrillation and poor rate control.

The half-life of digoxin may be significantly prolonged with renal impairment, so the maintenance dose may be lower and plasma monitoring may be required.

Common adverse effects: Nausea and vomiting, visual disturbances (i.e. blurred vision), bradycardia, dizziness, anorexia.

Ivabrabine

Ivabradine is a direct sinus node inhibitor and slows heart rate. It can be used in patients with CHF who are in sinus rhythm and are intolerant of beta blockers, or have poor rate control despite taking the maximum tolerable beta blocker dose.

When added to other therapies, it may reduce CHF-related hospitalisations. Ivabradine is absorbed best when taken with food.

It is hepatically cleared, thus caution needs to be exercised when taken concurrently with cytochrome P3A4 inhibitors (i.e. clarithromycin, itraconazole, ketoconazole).

Common adverse effects: Transient areas of enhanced brightness in the visual field, especially in the first two months of treatment, bradycardia (dose-related), dizziness.

Drugs to avoid in CHF include;

- Anti-arrhythmic agents (except beta blockers and amiodarone)
- Verapamil, diltiazem (in most cases)
- Tricyclic antidepressants
- Nonsteroidal anti-inflammatories and COX-2 Inhibitors
- Pioglitazone, rosiglitazone
- Corticosteroids
- Moxonidine (has been associated with increased mortality in CHF patients)
- Trastuzumab (has been associated with the development of reduced Left Ventricular Ejection Fraction and CHF), and
- Preparations with high sodium load (i.e. many soluble preparations, including soluble Panadol, Ural, Berocca).

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An Update on Crohn's Disease

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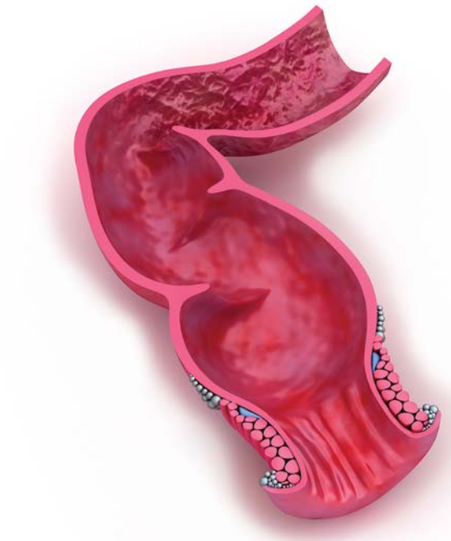

Crohn's disease is an inflammatory bowel disease that can affect any part of the gastrointestinal tract. Inflammation can be focal or widespread. Abscesses, internal and external fistulas, and bowel obstruction may arise.

It mainly presents as abdominal pain, diarrhoea, fever, weight loss, or iron deficiency. Causes include bacteria, genetic (20-30% have a family history), lifestyle, environment, or random causes. Crohn's disease affects the same number of females as it does males. The peak age of onset varies between 15-25 years of age. Incidence has doubled since the 1970's (this is not just due to better recognition).

Crohn's disease is diagnosed when typical features are seen in a combination of colonoscopy, histological and radiological investigations. Faecal biomarkers (calprotectin and lactoferrin) can help diagnose Crohn's disease. This provides a non-invasive option, however faecal testing is not funded by Medicare so it is not commonly used. Patients may choose to pay the full cost for this test because it eliminates the need for a colonoscopy. It also has a potential role in detecting flares once diagnosis is established.

It has been shown that morbidity is increased with Crohn's disease, however life expectancy is unchanged. That is why treatments aim to improve the quality of life, rather than quantity.

The severity of the disease and the site(s) of the affected bowel determine which drugs may be used and their route of administration or formulation. The aims of therapy are to induce and then maintain remission, and to prevent relapse. It is also important to prevent complications and nutritional deficiencies.

Mild to Moderate Crohn's Disease

Oral or parenteral corticosteroids (e.g. prednisolone, hydrocortisone), are the most effective first-line drugs for treating active Crohn's disease. Response rates in most clinical trials are about 60-70% at 12-16 weeks. Corticosteroids are effective for inducing remission in acute disease but ineffective as maintenance. Once in remission (which usually takes 7-14 days), the dose should be reduced gradually according to disease severity and patient response. Rectal corticosteroids are effective for distal colonic inflammation.

5-Aminosalicylates (5-ASAs) such as sulphasalazine and mesalazine are commonly used as first-line treatments. They are used to induce remission in mild-to-moderate disease. Efficacy in maintaining remission is controversial. However, they may have a limited effect on the rate of postoperative recurrence of small bowel disease.

Thiopurines (azathioprine, mercaptopurine) are used for inducing and maintaining remission, decreasing postoperative relapse in complex disease, and for their corticosteroid-sparing effect in patients with corticosteroid dependent or resistant disease. Although onset of action may be up to three months, they may be used as adjunctive treatment in active disease. There are no direct comparisons of azathioprine with mercaptopurine, but some patients who are unable to tolerate one agent may tolerate the other.

Methotrexate is effective for inducing remission and/or preventing relapse and is mainly used in patients refractory to, or intolerant of, thiopurines. Although oral dosing is more convenient, parenteral administration may be more effective.

In clinical trials metronidazole and ciprofloxacin, alone or in combination, have been shown to have a limited effect when used in active Crohn's disease of the colon. These antibiotics are sometimes added to corticosteroids, or less commonly to 5-ASAs, although there is no evidence to support these combinations. Antibiotics are considered a first-line agent by some clinicians, or they may be reserved for patients not responding after 4-6 week of a 5-ASA. Their use is strictly empiric.

With any of these drugs, 8-16 weeks of treatment may be required. Responders are converted to maintenance therapy.

Severe Crohn's Disease

Initial therapy for severe Crohn's disease includes intravenous corticosteroids. Fluid, electrolyte, or blood replacement may also be required. The optimal duration of intravenous corticosteroid therapy is not known, but it is generally given for 3-7 days. Oral corticosteroids should be substituted when disease activity has subsided. Patients not responding to corticosteroids, or those who cannot be tapered, should receive a thiopurine or methotrexate.

As the onset of action of thiopurines and methotrexate may be delayed, therapy should be continued with thiopurines for at least 3-6 months, and methotrexate for 2-3 months, before they are deemed to have failed. The benefits of thiopurines extend for at least three or four years of therapy and probably longer. There is less information about the duration of benefit of methotrexate.

Tumour Necrosis Factor (TNF)-alpha antagonists (infliximab, adalimumab) are preferred by some as second-line agents after corticosteroids but are contraindicated with active infection. They may be considered for moderate-to-severe disease (including fistulae) unresponsive to conventional therapy. The cost-to-benefit ratio limits the use of these agents. Clinical trials have shown response rates of 60-70% in patients with refractory active Crohn's disease.

Broad-spectrum antibiotics (metronidazole and/or ciprofloxacin) are often given, especially if transmural complications (e.g. abscesses or fistulas) are suspected.

Maintenance Therapy for Crohn's Disease

Most patients need ongoing therapy to maintain remission. 5-ASAs are first-line drugs for maintenance therapy. Patients who require only a 5-ASA to achieve remission can be maintained on this drug. There is good evidence that thiopurines are effective for maintenance, and should be used in patients who have frequent relapses, or are corticosteroid-dependent. If these therapies are not tolerated or are ineffective, methotrexate may be considered.

TNF-alpha antagonists have also been shown to be effective for maintaining remission in luminal and fistulising Crohn's disease. Patients who respond to infliximab for acute disease but who are not well maintained on antimetabolites may stay in remission with repeat doses of infliximab at eight week intervals.

Surgery

Even though about 70% of patients ultimately require surgery, it is always performed reluctantly. It is best reserved for recurrent intestinal obstruction or intractable fistulas or abscesses. Resection of the bowel may alleviate symptoms but does not cure the disease, since Crohn's disease is likely to recur even after resection of all clinically apparent disease.

Ultimately, further surgery is required in nearly 50% of cases. However, recurrence rates appear to be reduced by early postoperative prophylaxis with mercaptopurine, metronidazole or possibly a 5-ASA. When surgery is performed for appropriate indications, almost all patients experience an improved quality of life.

Future Trends in Therapy

Quality of life is now paramount. Earlier, intensive therapy is being considered by many clinicians. Early diagnosis and prognosis is important because complications accumulate overtime, therefore it is essential to start treating as soon as possible to prevent complications. A study which followed patients over an extensive period found that over 20 years, there was an 88% risk of developing stricturing (18%) or penetrating (70%) disease.

The *'Top Down'* method of using third-line biologicals early on is becoming more attractive. This method tries to eliminate steroids (or perhaps just use short courses initially during flare ups) and recognises that thiopurines take 6-8 weeks to give any benefit, which may be too late. PBS restrictions currently pose a challenge for this method; however pressure is being applied to allow the use of these more expensive drugs in patients who have poor prognosis.

Early surgery is another option being looked at.

There is also a stronger push for patients to see specialists earlier. Currently, most patients will see their general practitioner for 'flare ups' and after two or more flare ups, they are referred to the specialist. Seeing a specialist while in the remission phase (i.e. before the second flare up) allows more time to make treatment decisions and improve the patient's quality of life.

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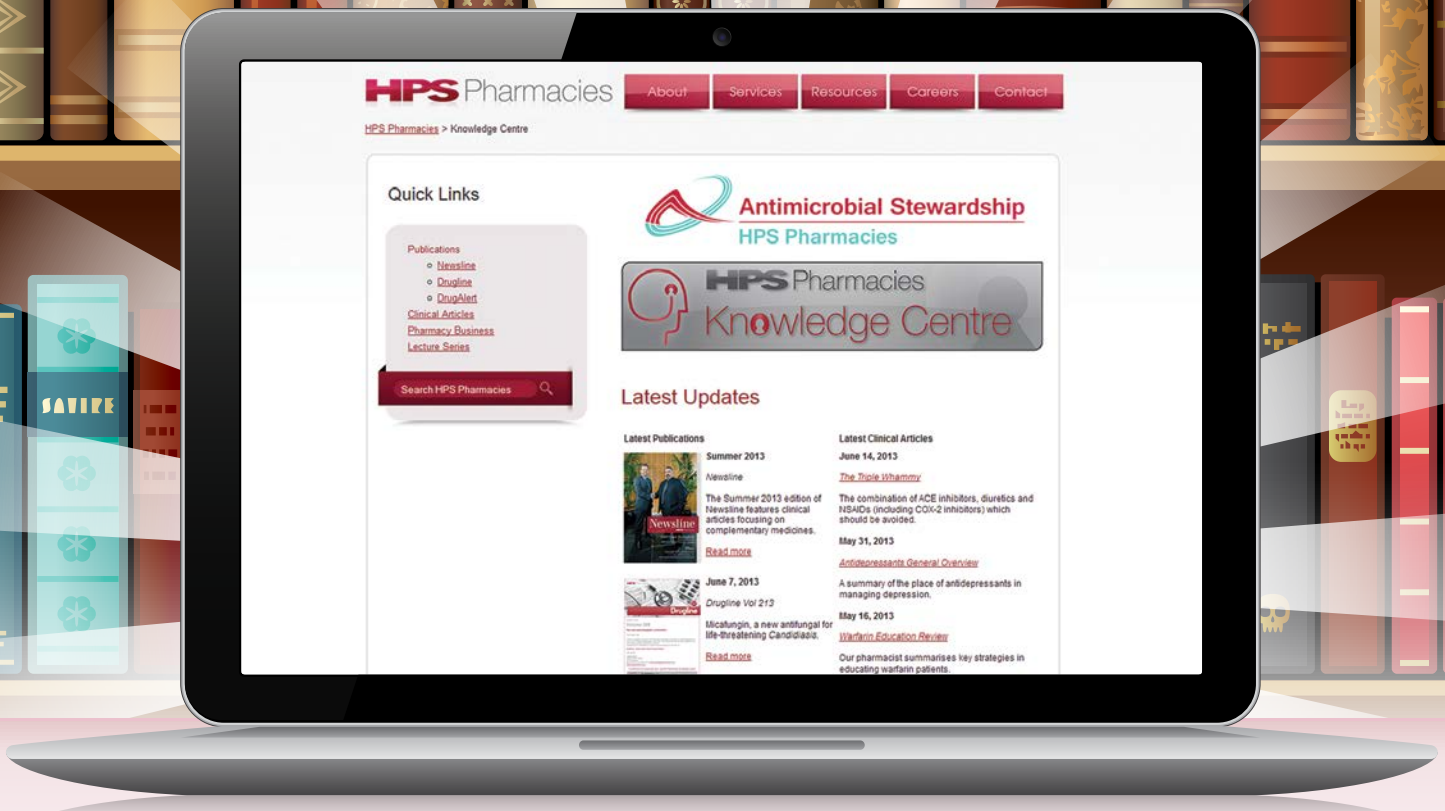

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