Spring 2013

Newsline

HPS Pharmacies

Calvary Health Care Riverina

Welcomes HPS Pharmacies as its on-site pharmacy service provider

Plus:

HPS Pharmacies' Board reappoints its Chief Executive Officer, and

Giving back to the business environment

HPS Pharmacies

Sponsorship

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

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(Left to right) Joanne Williams, Chief Executive Officer at Calvary Health Care Riverina, with Alan Tuxford, Regional Operations Manager – VIC/TAS at HPS Pharmacies.

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Message from Tony Wyatt CEO

In the past nine months, our business has experienced stable growth, delivering significant value for HPS Pharmacies and further cementing our business as the leader in the pharmacy industry.

In line with our operational growth, the business engaged a dedicated resource to implement and monitor internal auditing processes to strengthen practices at all sites. In further support of this, the formation of HPS' Professional Services Committee aims to enhance value delivered to clients through the standardisation of professional services. Both initiatives provide an official framework for HPS to challenge its current practices and analyse opportunities for improvement and innovation.

It is this commitment to innovation, and dedicated industry support that underpins HPS Pharmacies' success and focus to remain at the forefront of progression within the industry. In August, HPS Pharmacies exhibited its strong ties, and continued support at two key industry conferences; as associate sponsor of the Correctional Services Healthcare Summit, and keynote speaker sponsor of the Catholic Health Australia Conference.

The Correctional Services Healthcare Summit also afforded the ideal platform to launch our new electronic charting software program, MACI (Medication Administration Client Interface). For more information on MACI, contact HPS Pharmacies' Partner/General Manager – Hospitals, Tin Huynh, at tin.huynh@hpspharmacies.com.au.

Further to our announcement in May regarding the successful negotiation of HPS Pharmacies inaugural Enterprise Agreement (EA) for Pharmacists, we are pleased to communicate the commencement of the process towards forming a new EA for our Pharmacy Technicians and Couriers. The process is currently underway and signifies the second generation of Enterprise Agreements for HPS Pharmacies, further solidifying the business' position as the employer of choice within the pharmacy industry.

I anticipate the last few months of 2013 will be highly successful as our charter for growth continues to come to fruition. We look forward to continuing our journey with you, as our valued clients and associates, during this time and are truly excited about what the future holds for HPS Pharmacies.

Tony Wyatt
Partner/Chief Executive Officer

Message from Steve Yeo COO

As we head towards the final quarter of 2013, I take a moment to reflect on HPS Pharmacies' recent achievements; specifically growth realised through the successful re-signing of numerous contracts over the past twelve months. Resultantly, HPS has further solidified its national footprint through the addition of several new sites to the HPS portfolio this year.

Most recently, HPS Pharmacies is excited to announce the opening of its regional on-site pharmacy at Calvary Health Care Riverina in Wagga Wagga, NSW. HPS has a longstanding relationship with Little Company of Mary Health Care, and the opening of HPS – Riverina has further strengthened the partnership and broadened it beyond South Australia. To read more, please turn to page 6.

Further to the announcement in June regarding HPS Pharmacies' recently launched eLearning solution to the business, I am pleased to communicate the overwhelmingly positive feedback we've received regarding HPS' industry leading employee induction. This professional induction has proven successful in introducing new employees to HPS Pharmacies' strong culture and provides detailed information across various aspects of the business to deliver a smooth transition to joining the team. We are proud to have developed a dedicated communication tool encapsulating the essence of HPS Pharmacies, further solidifying HPS Pharmacies' position as the employer of choice within the industry.

As a leader in Australia's healthcare industry, we understand that how we look after our clients, our workforce, our environment and our community is vital to our success. With that in mind, HPS Pharmacies is proud to launch its Corporate Social Responsibility (CSR) agenda. HPS Pharmacies considers its activities in this area a benchmark for the company's operations, as it continues to invest in community and environmental stewardship. HPS Pharmacies' proactive approach ensures continued progressiveness, leading the pharmacy services market in the field of Corporate Social Responsibility. To read more, please turn to page 10.

We are excited about what the future holds for HPS Pharmacies and look forward to delivering greater service enhancements to our clients and employees during this next exciting period for HPS Pharmacies.

Steve Yeo
Chief Operating Officer

This page: Alan Tuxford, Regional Operations Manager – VIC/TAS at HPS Pharmacies, with Joanne Williams, Chief Executive Officer at Calvary Health Care Riverina.

Cover page: Joanne Williams, Chief Executive Officer at Calvary Health Care Riverina, with Alan Tuxford, Regional Operations Manager – VIC/TAS at HPS Pharmacies.

HPS On-site at Calvary Health Care Riverina

It is with great pleasure and excitement that HPS Pharmacies announces the opening of its new on-site pharmacy at Calvary Health Care Riverina in Wagga Wagga, NSW.

In addition to servicing the hospital, the contract includes delivering services to an off-site day surgery, and signifies the business' first partnership with a Calvary hospital outside of South Australia.

HPS Pharmacies' Regional Operations Manager, VIC/TAS, Alan Tuxford, says "securing this contract delivers significant value for HPS Pharmacies and expands our growth in regional healthcare.

"Regional healthcare presents unique challenges to service providers, and HPS Pharmacies aims to overcome these by working collaboratively with Calvary Health Care Riverina to deliver continuous improvements to patient care."

HPS Pharmacies has a longstanding relationship with Little Company of Mary Health Care, adding further value to the partnership late last year through the proactive re-signing of its contract and extension of services.

Calvary Health Care Riverina is a 104-bed hospital, providing a full range of both surgical and medical services to the Wagga Wagga and broader community; including cardiac, acute surgical and orthopaedics, critical care, and neurological services.

"HPS Pharmacies commenced on-site pharmacy services to the hospital in August, taking over from the previous service providers, to introduce clinical services and deliver improved dispensing and imprest management," says Alan.

> *We are delighted with the delivery of enhanced clinical pharmacy services at Riverina to further improve patient interaction, especially in regards to medicine management.*
>
> – Joanne Williams, Chief Executive Officer, Calvary Health Care Riverina

"We are pleased to have maintained many of the hospital's existing pharmacy employees, as well as increase staffing levels to facilitate the expanded services to both the hospital and day surgery," he says.

HPS – Riverina's Pharmacist In-Charge, Jane Smithard, says HPS Pharmacies has been incredibly supportive, facilitating a seamless transition of services to the hospital.

"I am excited by the improvements made by HPS Pharmacies to increase staffing levels, allowing us to deliver clinical services for patients moving forward, and further strengthen support for the hospital's re-accreditation in medication safety standards," says Jane.

Calvary Health Care Riverina's Chief Executive Officer, Joanne Williams, is excited to be working closely with HPS Pharmacies to maximise the efficient use of resources, particularly in the current political and financial climate.

"HPS Pharmacies has a proven track record for the provision of high quality pharmacy services to many of Calvary's hospitals, and we are delighted with the delivery of enhanced clinical pharmacy services at Riverina to further improve patient interaction, especially in regards to medicine management," she says.

HPS Pharmacies' System Training Consultant, Angie Lawson, was instrumental in the project and says several corporate employees from varying departments travelled to Wagga Wagga to assist with the transition.

"We understand the importance of delivering a seamless transition to our clients and are elated to receive such positive feedback from employees at Calvary Health Care Riverina. The HPS Pharmacies team has taken key learnings from projects similar in nature, and has delivered above expectations.

"Working alongside the pharmacy's existing employees benefited the transition greatly as they were very familiar with current processes, allowing us to make preparations in advance."

The success of the transition also relied on effective communication with the hospital staff, achieved through a series of nurse educational sessions held by HPS Pharmacies, allowing questions to be answered and for HPS' employees to speak face-to-face with nursing staff about the service changes. It also facilitated a consultative channel for feedback where ongoing issues experienced prior to HPS Pharmacies commencing services could be discussed and problem solved.

"Throughout the transition process, HPS Pharmacies have gone out of their way to consult with our Managers around service delivery, expectations and setting priorities for the establishment of their service. This consultation process is vital to ongoing service delivery and understanding between both parties to ensure the highest quality patient care," says Joanne.

Feature Article

leadership that i

This page: Tony Wyatt, Partner/Chief Executive Officer at HPS Pharmacies.

www.hpspharmacies.com.au

HPS Reappoints Tony Wyatt as Chief Executive Officer

It is with great pleasure that HPS Pharmacies' Board announces the reappointment of Tony Wyatt as Chief Executive Officer for a further two year term.

Dr Andrew Holsman, Chairman of the HPS Pharmacies Board, shares the Board's delight at Tony's reappointment as Chief Executive Officer, and its confidence in the business' future sustainability and growth prospects despite the numerous challenges arising from changes in Government health policy.

"In a time of great change, Tony's experience and leadership is essential to our business aspirations. We congratulate Tony on his successful reappointment and look forward to HPS Pharmacies' next phase under the assured direction, guidance and experience of a committed and passionate Chief Executive Officer and his team," says Dr Holsman.

Throughout his first term as Chief Executive Officer, Tony has achieved numerous successes, including but not limited to;

- Future proofing the business through the successful re-signing of the national Healthscope contract
- The successful re-signing of the national Little Company of Mary contract
- The re-signing of the St Andrew's Hospital contract
- The repositioning of HPS Pharmacies in the national industry through Tony's excellent work on chemotherapy drugs
- The development of a new corporate structure and a clearly defined strategic direction
- The development of a highly skilled, highly motivated, and high achieving Executive team
- Negotiation and implementation of HPS Pharmacies' Pharmacist Enterprise Agreement

Samantha Greaves, Partner, Board Member, and HPS Pharmacies' Strategic Projects Manager says "over the last two years, Tony has piloted the HPS Pharmacies Executive team with clear focus and determination. We look forward to continuing to work with Tony to meet the strategic goals of the business."

Additionally, Janene Garde, Partner, Board Member, and HPS Pharmacies' Clinical Publicist, believes the future will see HPS apply its considerable expertise to further develop innovative solutions for the benefit of clients and their patients.

Tony has an incredible depth of pharmacy experience spanning 34 years in the industry, and has been part of HPS' management team for more than eight years, appointed to Chief Executive Officer in July 2011.

> *"...[we] look forward to HPS Pharmacies' next phase under the assured direction, guidance and experience of a committed and passionate Chief Executive Officer and his team."*
>
> – Dr Andrew Holsman, Chairman, HPS Pharmacies Board

Prior to his equity partnership with HPS, Tony owned and operated various hospital pharmacies across Melbourne, and held the position of Managing Partner with a large hospital pharmacy business from 1998 to 2003.

Since 2003, Tony has gathered a wealth of experience within HPS Pharmacies, first as Pharmacist In-Charge at Brunswick, then as State Manager for Victoria and Tasmania. Tony has played an integral role in developing the company since 2009, acting in the position of Joint Chief Operating Officer, providing focused and competent leadership whilst the business considered its long term CEO requirements.

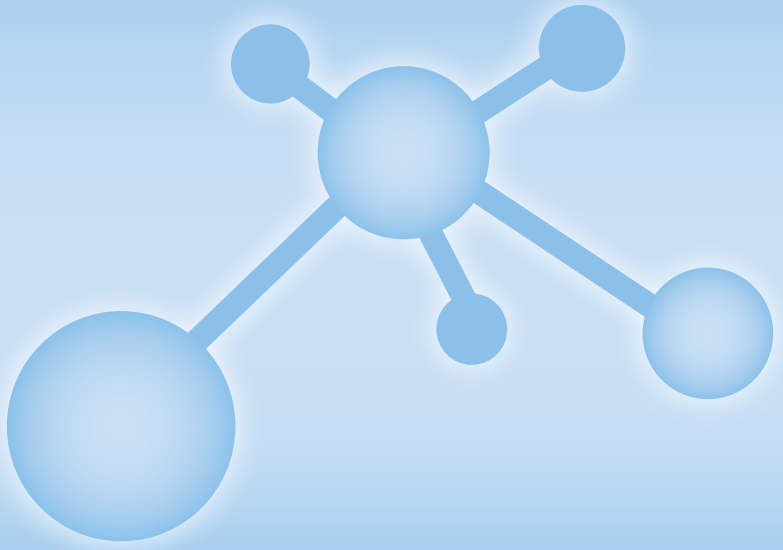
In addition to these responsibilities, Tony has been a member of the HPS Pharmacies Shareholder Committee since 2007, and a Board Member since 2005. Other accolades include a Board Member of St Paul's Drug Rehabilitation Centre as a Non-Executive Director, guest speaking at the AUSMED/ANF study day, and graduate of AICD in 2007.

HPS Pharmacies' Partner, Board Member and General Manager – Hospitals, Tin Huynh, says "Tony's reappointment as CEO reaffirms the Board's confidence in Tony to lead the business and execute the strategic plan in the coming years. His reappointment ensures HPS retains the valuable skills and experience of Tony to lead us through a challenging, yet exciting, period for HPS Pharmacies and the pharmacy industry in general."

On behalf of the entire HPS Pharmacies business, we congratulate Tony on his reappointment to the position of Chief Executive Officer as we look towards his next term with much excitement and anticipation as he guides the business to future successes.

Feature Article

Society



Environment

Business

Giving Back to the Business Environment

> *HPS Pharmacies has pledged significant financial contributions...totalling in excess of $460,000.00.*

HPS Pharmacies' commitment to business sustainability is unwavering, and embraces environmental and community stewardship as both a necessary contemporary issue and core business practice.

Corporate Social Responsibility (CSR) provides a tangible framework for HPS Pharmacies to successfully and harmoniously operate within.

Steve Yeo, Chief Operating Officer says as an integral member of today's rapidly changing community, HPS Pharmacies places great importance on not just what we do, but how we do it.

"As a leading provider of healthcare in Australia, HPS Pharmacies recognises the incredible contribution that can be made by having a robust and relevant CSR program," he says.

"We are continually striving to adapt to the ever changing needs of society and contribute to the overall health of the environment in which we operate, lessening our impacts via our supply chain and product lifecycle."

HPS Pharmacies' holistic view of its business activity is depicted in the triple bottom line approach to CSR, which recognises three streams – society, environment and business.

Steve says "HPS Pharmacies is focused upon ensuring that its environmental footprint is minimised, its social engagement is rewarding to all parties, and that its business is sustainable into the future."

HPS Pharmacies' social program has a strong clinical and health focus, representative of the whole life journey, with an emphasis on extending and enhancing human life. This commitment is underpinned through business relationships, supporting clients to strengthen their health systems.

As part of its social agenda, HPS Pharmacies has pledged significant financial contributions to various recipients during the last financial year, totalling in excess of $460,000.00. Donation beneficiaries include; Mary Potter Foundation, Ovarian Cancer Research Foundation, Father Bob Macquarie Foundation, Bowel Cancer Australia, Cancer Council, St Helen's Cancer Ward Upgrade Appeal, Calvary Education Fund, St Vincent's Toowoomba Corporate Golf Day, St Andrew's Golf Classic, Foundation 21, Lifeline, Kids Under Cover, Beyond Blue, Red Shield Appeal, Alzheimer's Australia, and Act for Kids, to name but a few.

From an environmental angle, HPS Pharmacies has assessed its supply chain, understanding that a truly accountable business acknowledges the impacts their suppliers have on their people, environment and communities. HPS Pharmacies has challenged its suppliers and own business operations to promote sustainable business practice.

"We believe it is our obligation to ensure we are not only being environmentally conscious within our operations, but also that we are challenging all of our service providers within our overall supply chain to enhance their CSR focus as well," says Steve.

The ultimate goal relates to HPS Pharmacies' business channel, and ensuring the future longevity of the company, particularly with respect to providing jobs and custom for suppliers. HPS Pharmacies' business success allows for the building of mutually beneficial relationships, and steadfastly positions the company to support its suppliers, workforce and clients to the value of the entire community.

Catherine Riedel, Marketing Manager, says HPS Pharmacies' CSR agenda has been developed in consideration of the business' impacts on employees, suppliers, clients, and the communities in which we conduct business operations.

"Whilst developing the business' Marketing strategy, we realised the wealth of amazing activities that HPS already engages in. The CSR program provides a platform for the business to communicate these initiatives as we further integrate corporate responsibility across all our business interactions."

For more information on HPS Pharmacies' CSR program and activities, visit: *www.hpspharmacies.com.au/about/csr/*

HPS Pharmacies
Corporate Social Responsibility

From The Team

Jim Tavasci

Finance Manager

As another financial year passes, it brings with it a renewed focus on finalising HPS Pharmacies' end of year accounts. This detailed process consumes several months, and draws upon the Finance team's unwavering commitment and teamwork to ensure a smooth year end close.

Over the past twelve months, the Finance team has worked diligently to further enhance a number of finance related processes. These enhancements have proven to be vital developments for the business as it continues to progress through an exciting phase of growth.

In preparation for its journey through the 2013/14 financial year, HPS Pharmacies recently finalised its annual budgeting process. This process commenced with the HPS Pharmacies Regional Operations Managers and Business Analyst visiting each of their designated sites to set individual budgets. This collaborative approach unifies the business across various levels and fosters commitment and ownership at each of our sites.

All budgets have now received final approval from the HPS Pharmacies Board and have been fully implemented across each site nationwide. Having these budgets in place provides support to the business' decision-making during this new financial year, as well as the ability to set financial controls, monitor and report on the business' financial performance.

Samantha Greaves

Partner/Strategic Projects Manager

In addition to my position as Strategic Projects Manager, I have recently adopted responsibility for HPS Pharmacies' Risk Management portfolio. As "Risk Champion", my role is to engage and mobilise employees from across the business to play a role in risk management.

Working within the healthcare industry, a large proportion of our professional focus is upon clinical risks. However, we are also presented with risks to the broader business that may impact our long-term strategic goals, such as changing customer requirements, government policy or new technologies.

Additionally, we may experience operational risks related to the way in which we conduct general business, manage the company's finances or its people.

Over the past two years our structured, enterprise-wide approach to risk management has led to the establishment of a formal Risk Committee, which serves as a sub-committee of the HPS Pharmacies' Board. As an organisation, our collaborative approach to risk management allows for the identification and management of key risks and enables us to direct resources to where they are most effective.

Most often risk management is associated with avoiding unpleasant, costly, or unexpected surprises, however at HPS Pharmacies, we believe it can also assist the organisation in identifying significant opportunities.

Zeyad Ibrahim

National Oncology Manager

Recently HPS Pharmacies initiated a Professional Services Committee (PSC) responsible for guiding the business' quality standards to ensure the highest level of professional service to our clients. The committee was convened by our Executive team and has been established to oversee the critique, development and enhancement of professional service activities and programs for HPS Pharmacies.

The PSC aims to; improve and validate the professional standard of services across HPS Pharmacies in line with the current professional development of hospital pharmacy practice and regulatory framework, resolve important issues that require specialist expertise, knowledge and qualifications, and further develop a professional image of the business as a leader in the field of pharmacy services with exceptional expertise and qualifications.

Meeting on a monthly basis, the inaugural committee meeting was held in June and as Chairperson, I am excited at the prospect of the PSC developing and promoting high level professional and technical abilities aligned with industry and healthcare demands and standards.

Understanding the changing needs of our clients and the renewed industry emphasis on professional services, the dedication of a specific committee to centralise control of professional service activity and monitor quality standards, will ensure more effective compliance with regulatory changes, and deliver services nationally that are of industry standard.

Tin Huynh

Partner/General Manager – Hospitals

This August, HPS Pharmacies again showed its dedication to supporting the correctional healthcare industry as proud Associate Sponsors of the 4th Annual Correctional Services Healthcare Summit held in Melbourne. The summit provides networking opportunities and showcases industry innovations aimed at improving healthcare within the correctional setting.

HPS Pharmacies assumed a more prominent role at this conference, exhibiting its new correctional software program, MACI (Medication Administration Client Interface), in addition to a 30 minute presentation within the summit's program.

Leveraging our expertise in delivering pharmacy services to correctional facilities, HPS Pharmacies has garnered unique insight into the specific and specialised requirements in this area, and experienced first-hand the growth and transformation of the industry. The presentation featured this knowledgeable insight and highlighted HPS Pharmacies' trend analysis in determining the future needs, challenges and opportunities correctional facilities will face moving forward.

HPS Pharmacies has invested significant resources in the past twelve months to developing innovative solutions for our clients, and deliver service models that are tailored to meeting the unique needs of correctional facilities. Forecasting the future outlook of the industry ensures HPS Pharmacies remains leaders within the corrections market, and demonstrates our commitment to proactive preparedness to meet our client's changing needs.

Pharmacy Business

How can people access, and die from, synthetic drugs?

Australian medicines and poisons are separated into nine schedules according to the controls required for labelling, storing and supplying them. Schedule 9 lists those prohibited substances, such as cannabis, LSD, and heroin, which may be abused or misused.

The problem lies in the way the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) is structured, in that if an individual product has not been specifically included into a schedule, it is therefore unregulated, and uncontrolled. The synthetic drugs which have appeared in the media recently are chemicals that are structurally different from, but have similar effects to, the drugs they are mimicking.

Synthetic cannabinoids activate cannabinoid receptors to generate the euphoria, psychoactive effects, analgesia, and mood and behaviour regulation. Some synthetic cannabinoids have been registered as medicines: rimonabant (for obesity, now withdrawn), nabilone (for anorexia and emesis), and dronabinol (for multiple sclerosis and pain). Unscheduled synthetic cannabinoids with names like 'Kronic', 'Spice', 'Karma', 'Voodoo', 'Kaos', and 'K2' are sold over the Internet or through specialty stores as 'legal' recreational drugs.

The idea of extending the SUSMP to include these unscheduled products using terms such as 'analogue', 'derivative', and 'synthetic' has been explored, but decided against; because any definition which is broad enough for this purpose can conflict with the precision required under patent law; may not reflect the similarities and differences between structure, pharmacology, and toxicology; and because our current system is thought to be working.

Eight new synthetic cannabinoids were added to Schedule 9 in 2011 and another nine in 2012. There are surely more to follow.

References:

1. Delegates of the Secretary to the Department of Health and Ageing. *Final Decisions & Reasons for Decisions*. Canberra: Medicines and Poisons Scheduling Secretariat. July 2011.
2. Delegates of the Secretary to the Department of Health and Ageing. *Reasons for scheduling delegate's interim decision and invitation for further comment*. Canberra: Medicines and Poisons Scheduling Secretariat. May 2013.
3. Department of Health and Ageing. *Poisons Standard 2012*. Canberra: Australian Government; June 2012.

Accreditation in Practice

Within the fifteen criteria for medication safety in the *Hospital Accreditation Workbook* are several that involve informing, educating, and planning medication management in partnership with patients in ways that meets their particular needs. In practice, this can be challenging and certainly requires more than expedience and efficiency.

Take for instance a 73 year old widower who has intraocular lenses implanted, seemingly a simple day surgery, requiring discharge with antibiotic and anti-inflammatory drops. This stressor, however, added to the inexorable progression of Parkinson's disease, could rob him of his fragile independence.

Post-anaesthetic confusion, poor vision, and clumsiness mean that he can't easily remember or implement his instructions, or read the *Consumer Medication Information* provided. Fear that eye discomfort indicates infection means that drops are continued longer and more frequently than prescribed, if they aren't forgotten along with his other medicines.

It takes a diligent pharmacist to recognise that dispensing records don't reflect the prescribed dosages, and invest the effort to find a solution that our widower can understand and implement consistently.

Tears Again® offers a lateral solution to maintain hydration and reduce eye discomfort. Application via a spray from 10cm doesn't need the same aseptic care or dexterity as drops. Whether for comfort or fear, it can be safely used frequently, and doesn't matter if they are forgotten (as that indicates comfort). Confidence is revived, and a decluttered mind remembers to use his new dose administration aid. Another nursing home placement avoided, and one relieved patient!

Further Reading:

1. Poupoulas V. *From Compliance to Adherence to Concordance: The Evolution from Paternalistic Medicine to Patient Empowerment*. HPS Pharmacies Newsline 2013; 2: 18–19.
2. Ncube B. *Dry Eye Syndrome*. Adelaide: HPS Pharmacies; 2013. Available from <www.hpspharmacies.com.au/knowledge-centre/clinical-article-dry-eye-syndrome>. Accessed 19 July 2012.
3. Australian Commission on Safety and Quality in Health Care. *Hospital Accreditation Workbook*. Sydney. ACSQHC, 2012.

Patent vs Free Market

Governments everywhere trade off economic reality against long-term good, and the balance between patent protections and free markets are no different.

Patents are there to stimulate the research and development of new therapies and support enterprise, by guaranteeing the enjoyment of all the profits that good marketing of a new medicine can generate for up to 25 years.

Canny pharmaceutical companies subsequently service shareholder, rather than patient obligations by "evergreening" their products with new patent applications, usually for small changes in formulation or systems of administration.

India has recently affirmed their opposition to "evergreening" by denying patent applications for Glivec®, Sutent®, and Pegasys®. It would seem that Glivec® has no place in the Indian market where generic pharmaceutical brands supply 300,000 consumers at around one-tenth of the originator's price.

Gardasil® is an example of the vast resources required to take a drug to market. The first patent application for Gardasil® was filed in 1991, before research findings could be safely shared with, and scrutinised by, the scientific community prior to its official release in 2006. During this period there were international patent applications and IP court battles.

In 2007 it celebrated sales of US $1.5 billion and is now approved in 121 countries.

Under the patent application system, research is driven by the achievable returns. Many medicines have multi-faceted indications, such as antiepileptics that can be used for mood stabilisation and pain management.

Pharmaceutical companies rarely invest in further research for new indications, leaving clinicians to prescribe off-label from hearsay, and restricting patient access to government subsidies for these indications.

Peter Mansfield, sceptic, recommends separation of research and distribution. He suggests that the government could afford to fully fund independent research from the savings achieved by truly competitive pricing in a patent and subsidy free environment.

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

Opportunity Within Challenge

Whilst many of us can describe trends that will shape the environment of our future, whether physical or economic, KPMG have gone so far as to itemise how nine out of ten "megaforces" will challenge healthcare.

Population trends show a wealthier middle class who live longer and so demand more of healthcare services to treat chronic diseases. To match the Western model of consultation, India would require 800,000 new clinicians, where in fact shortages are getting worse.

Novel service models in the UK (using telehealth and telecare) may suit better, as they demonstrated reductions of 20% in emergency admissions, 14% in elective admissions, and 45% in mortality rates.

The demand for freshwater is expected to exceed supply by 40% within 20 years, and the quantity used by healthcare facilities and pharmaceutical companies, who develop and manufacture medicines, will put significant pressure on availability, quality, and drive soaring costs.

We learn that the contribution to greenhouse gas emission by healthcare now tops 5% in the EU and is 8% in the US. The report goes on to describe projects that have significantly reduced energy consumption; retrofitting equipment and using simple energy saving measures saved the Royal Free Hospital in the UK EUR1.8 million per annum, and 100 hospitals in São Paulo reduced energy use by 25%, desirable in any economy.

The "megaforces" may be the stimulus to change the status quo in a world where 1.9 million premature deaths annually are attributed to simply breathing the smoke from cooking fires.

Reference:

1. KPMG International Cooperative. *Care in a changing world: challenges and opportunities for sustainable healthcare.* Zurich: KPMG International; 2012. Available from <www.kpmg.com/global/en/issuesandinsights/articlespublications/care-in-a-changing-world/pages/default.aspx>. Accessed 15 July 2013.

Linagliptin – An Incretin-Based Therapy for Type 2 Diabetes Mellitus

Dina Dinh, Clinical Pharmacist
HPS – Melbourne Private, Victoria

It is estimated that 346 million people worldwide have diabetes. Of this figure, Type 2 Diabetes Mellitus (T2DM) comprises 90% of people with diabetes. T2DM is associated with chronic microvascular and macrovascular complications and management is further complicated in special patient populations such as in those with Chronic Kidney Disease (CKD).

When determining appropriate therapies for T2DM in patients with CKD, individualisation of treatment is necessary and should take into account comorbidities, the history of hypoglycaemia, hypoglycaemia (un)awareness, patient education, motivation, adherence, age, life expectancy, and other medications. Drug therapies often require dose modification, or are not suitable in patients with severe renal impairment as drug clearance is reduced, leading to prolonged exposure to the drug or its metabolites. Other challenges are the adverse effects, particularly hypoglycaemia, and effects on weight, from traditional oral anti-diabetic therapies.

Metformin, a biguanide oral hypoglycaemic, is considered first-line treatment of T2DM, however its use is limited in patients with CKD (particularly moderate to severe CKD) as the plasma half-life is prolonged and renal clearance is reduced, resulting in an increased risk of accumulation and lactic acidosis.

A greater understanding of glucose homeostasis and its role in T2DM novel drug therapies, and in particular the incretin-based therapies, provides further options for prescribers. Linagliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor approved for the treatment of T2DM, does not require dose reduction in renal impairment, and as such may be a valuable addition in the renally impaired population.

Linagliptin (Tradjenta®, Boehringer Ingelheim Pharmaceuticals) is a competitive, reversible inhibitor of the DPP-4 enzyme which is involved in the degradation of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

In humans, eating promotes the secretion of gastrointestinal hormones involved in gut motility, gastric acid and pancreatic enzyme secretion, as well as the stimulation of insulin secretion. GLP-1 is found in the enteroendocrine L cells of the distal ileum and colon, and is secreted upon the ingestion of food. It promotes satiety, reduces appetite, reduces gastric emptying, inhibits glucagon secretion, enhances glucose-dependent insulin secretion by the ß-cells of the pancreas, and promotes ß-cell proliferation.

In addition, GLP-1 may lower postprandial hyperlipidaemia through inhibiting intestinal lipoprotein secretion, and may offer cardioprotection. DPP-4 inhibitors essentially reduce the breakdown of the incretin hormones, in particular GLP-1, thus enhancing glucose-dependent insulin secretion and inhibiting glucagon release. In patients with T2DM, the insulinotropic response to GLP-1 (compared with that of GIP) is preserved, and is the reason for the interest in developing agents targeting GLP-1.

Linagliptin's oral bioavailability of 30% is not affected by the presence of food. It is extensively protein bound (70%) in a concentration dependent manner, is rapidly absorbed and displays non-linear pharmacokinetics. Its long terminal half-life allows for once daily dosing and it is not extensively metabolised.

What sets linagliptin apart from others in its class is that most DPP-4 inhibitors are eliminated via the kidneys. In the case of linagliptin, elimination is predominantly via the hepatic biliary route, with approximately 85% eliminated in the faeces, and as such does not require dose adjustment in patients with renal impairment.

Linagliptin does not induce or inhibit the cytochrome P450 (CYP) isoenzymes, however it is a P-glycoprotein (P-gp) substrate, and inhibitors or inducers of P-gp may theoretically affect linagliptin's plasma kinetics. In vivo clinical data has not shown any clinically relevant effects on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin or oral contraceptives.

There is a low potential for drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter.

Linagliptin is generally well tolerated and, as with the other drugs in its class is reported to have a lower potential for hypoglycaemia and is also weight neutral. Traditional oral hypoglycaemics such as the insulin secretagogues (e.g. sulphonylureas) promote insulin secretion and so hypoglycaemia and weight gain can occur. There is a negligible risk of hypoglycaemia with the DPP-4 inhibitors because GLP-1 is released in a glucose-dependent manner, and in circumstances where there are low levels of plasma glucose the pharmacological effect is reduced.

Hypoglycaemia is more frequent when used in combination with a sulphonylurea, in the elderly, and renally impaired populations, so caution should be exercised when co-prescribing in these patients. Overall, linagliptin is safe and well tolerated.

In a study by Del Prato *et al*, linaglipton 5mg was given for 24 weeks to patients with T2DM who were either treatment naïve or had previously been treated with one oral anti-diabetic drug. Treatment with linagliptin resulted in a placebo-corrected change in HbA_{1c} from baseline of -0.69% ($p<0.0001$). Treatment with linagliptin also resulted in a greater reduction of fasting plasma glucose (adjusted mean change -1.3mmol/L; $p<0.0001$) and 2 hour postprandial glucose (adjusted mean change -3.2mmol/L; $p<0.0001$) when compared with placebo. Overall the study found that monotherapy with linagliptin when compared with placebo improved glycaemic control.

Taskinen *et al* showed that the addition of linagliptin to metformin resulted in a placebo-controlled reduction of 0.64% in HbA_{1c}, 1.2mmol/L in fasting plasma glucose levels and 3.7mmol/L in the two hour postprandial concentrations. This study also found that there was an improvement in the measures of ß-cell function.

Gomis *et al* compared the effect of linagliptin with placebo when administered once a day for 24 weeks in combination with pioglitazone and found that the combination reduced HbA_{1c} by a further 0.5% (1.1% combination therapy, 0.6% for monotherapy with pioglitazone). Fasting plasma glucose levels were greater in the linagliptin and pioglitazone group (-1.8mmol/L) when compared with the pioglitazone only group (-1.0mmol/L). An enhancement in ß-cell function was also seen.

Owens *et al* evaluated the use of linagliptin in combination with metformin and a sulphonylurea for 24 weeks. The rationale for this investigation was to look at the use of an agent with a complementary mechanism of action to further control blood glucose levels. It was found that at the end of the 24 weeks, the linagliptin placebo-corrected HbA_{1c} adjusted mean change from baseline was -0.62% ($p<0.0001$). Linagliptin also produced a greater adjusted mean change in fasting plasma glucose when compared with placebo (-0.7mmol/L; $p<0.0001$), and an improvement in markers of ß-cell function. There was an increase in hypoglycaemia seen in the linagliptin group; however the paper states that this increase is consistent with other studies using a DPP-4 inhibitor with a sulphonylurea.

Linagliptin is a novel DPP-4 inhibitor administered at a dose of 5mg once daily. By inhibiting DPP-4 enzyme degradation of GLP-1, the result is the enhancement of glucose-dependent insulin secretion and the inhibition of the release of glucagon. It displays non-linear pharmacokinetics, is highly protein bound, and has a long terminal half-life. Its lack of renal elimination gives it an advantage, especially in patients with severe renal impairment. It has limited drug-drug interactions which also makes it a favourable addition for patients with multiple comorbidities, such as those with T2DM and CKD, who require polypharmacy.

Linagliptin appears to be well tolerated and its lower risk of hypoglycaemia and weight neutrality makes it favourable in the treatment of T2DM. It has been demonstrated as being effective clinically as both monotherapy and in combination with other oral hypoglycaemics, and has also demonstrated improvement in ß-cell function.

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

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Rifaximin in Hepatic Encephalopathy

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Hepatic Encephalopathy

According to the *Australian Bureau of Statistics*, liver diseases ranked in the top 20 leading causes of death from 2002–2011. During this period, deaths related to liver diseases have increased by 17%, from 1,354 deaths in 2002 to 1,589 deaths in 2011. Hepatic encephalopathy (HE) is a complication from hepatic cirrhosis and it has imposed a significant burden on patients, their carers, and Australia's healthcare systems; as patients tend to lose the ability to care for themselves due to deteriorated cognitive function. They often require hospitalisation which puts a further strain on current shortages in healthcare professionals and hospital beds.

Hepatic encephalopathy is a neuropsychiatric syndrome which is caused by the inability of the liver to prevent ammonia from entering the blood circulation, leading to cerebral toxicity. In patients with chronic liver disease, precipitating factors such as metabolic stress, increase in gut protein, and central nervous system (CNS) depression by drugs or alcohol can lead to acute episodes of encephalopathy.

In the early stages of encephalopathy, patients can lose their cognitive abilities without any apparent signs. However, signs and symptoms of encephalopathy become increasingly apparent and debilitating as the disease progresses and the patient gradually loses both their cognitive and neuromuscular functions. Patients will develop mild signs and symptoms such as sleep disturbances, loss of concentration, drowsiness, tremor and ataxia in the early stages. As the disease progresses, patients can sometimes develop confusion, amnesia, and coma.

Treatment of Hepatic Encephalopathy

The current recommendation from *Therapeutic Guidelines Australia (TGA)* for treatment of acute hepatic encephalopathy is lactulose 30mL hourly. This is to induce rapid diarrhoea which subsequently reduces the absorption of ammonia by decreasing the number of colonic bacteria and lowering colonic pH. Once diarrhoea is achieved, administration frequency can be reduced to three or four times a day. In acute hepatic encephalopathy, precipitating factors such as electrolyte imbalances, infections, and removal of CNS depressing drugs need to be addressed.

To prevent recurrent episodes or chronic hepatic encephalopathy, lactulose 30mL three times a day is administered with the aim to produce two to three soft stools per day.

Rifaximin

In May 2012, rifaximin (Xifaxan®) became available in Australia following its registration with the TGA. It is now used as a second-line treatment for the prevention of recurrence of hepatic encephalopathy.

Rifaximin, a semisynthetic broad spectrum antibiotic, works against gram-positive and gram-negative bacteria in the gastrointestinal tract (GIT). It has very low oral absorption with a negligible plasma level after administration; therefore rifaximin acts locally in the gastrointestinal tract, targeting GI flora. It is administered orally twice a day. No dosing adjustment is required in patients with hepatic insufficiency due to its low oral absorption.

A randomised study has been conducted which enrolled 299 patients who were in remission from recurrent hepatic encephalopathy due to cirrhosis. Study subjects were randomly assigned to either receive rifaximin 550mg or placebo twice daily for six months or until recurrence of hepatic encephalopathy. During this trial 22.1% of subjects who received rifaximin developed breakthrough hepatic encephalopathy compared to 45.9% in the placebo group. 13.6% of hospitalisations due to an hepatic encephalopathy episode were from the rifaximin group and 22.6% from the placebo group recorded from this trial. The trial demonstrated that rifaximin reduces the risk of recurrence of hepatic encephalopathy by 23.8% and the risk of hospitalisation by 9%.

Reduced hepatic encephalopathy recurrence and hospitalisation would improve patients' quality of life and subsequently reduce financial cost of the disease to the healthcare system. However, more than 90% of patients in both groups received lactulose concomitantly. Thus, the benefit from rifaximin alone was not able to be determined from this trial.

Side effects reported in this trial which had higher occurrence in the rifaximin group were anaemia, ascites, vomiting, dizziness and peripheral oedema. Two cases of clostridium difficile infection were also reported in the rifaximin group where there were none reported in the placebo group. Patients should be warned of this side effect to ensure that they seek medical attention without delay if clostridium difficile associated diarrhoea is suspected.

Another concern with long term use of rifaximin is the development of drug resistant bacteria, including *Staphylococcus aureus*. Therefore, rifaximin should only be used as a second-line treatment where other treatments have failed or are contraindicated.

Although rifaximin is the only treatment that has demonstrated a reduction of recurrence of hepatic encephalopathy, and hospitalisation due to hepatic encephalopathy, it is not currently listed on the *Pharmaceutical Benefit Scheme (PBS)*. Therefore, patients would currently have to pay several hundred dollars per month which limits the accessibility for pensioners or low income households. The *Pharmaceutical Benefits Advisory Committee* made a positive recommendation for the listing of rifaximin on the PBS at the April 2013 meeting. They recommended listing based on current high clinical demand and that this treatment is superior to the existing treatment.

In conclusion, based on currently available data, rifaximin and lactulose used concomitantly can reduce the recurrence of hepatic encephalopathy and reduce the risk of hospitalisation due to hepatic encephalopathy. Listing of rifaximin on the PBS will allow patients access to this treatment at an affordable price, improving their quality of life and reducing the burden on their community.

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Dapagliflozin – A Novel Way to Control Blood Glucose

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The kidneys play an important role in glucose homeostasis by reabsorbing glucose from the glomerular filtrate back into the blood. Under normal conditions, almost all of the filtered glucose is reabsorbed and returned to circulation in the proximal convoluted tubule of the nephron. This glucose reabsorption takes place with the help of sodium-glucose co-transporters (SGLTs) in conjunction with facilitative glucose transporters (GLUTs).

The sodium-glucose co-transporter SGLT2, which is found primarily in the S1 segment of the proximal convoluted tubule, is predominantly responsible for this process, accounting for 90% of glucose reabsorption via the kidneys. This reabsorption of filtered glucose continues despite the presence of hyperglycaemia in Type 2 Diabetes Mellitus.

Selective inhibition of SGLT2 offers a novel approach towards treatment of hyperglycaemia in Type 2 Diabetes.

Dapagliflozin is one such reversible competitive inhibitor of SGLT2 and the only one in this new class of anti-diabetic drugs that is licensed for use in Australia. Another drug in the SGLT2 inhibitor class, canaglifozin, has recently been recommended for approval in the United States of America but is not yet available for use.

Dapagliflozin improves both fasting and postprandial glycaemic control in patients with Type 2 Diabetes Mellitus by reducing renal glucose reabsorption, thereby leading to urinary glucose excretion (glucuresis).

This glucuretic effect is observed following the first dose and continues for the duration of the treatment. Dapagliflozin is 1,000-3,000 times more selective for SGLT2 than for SGLT1, SGLT1 being the major transporter for glucose reabsorption in the gut.

Treatment options for Type 2 Diabetes have thus far focused on the secretion and/or action of insulin. The effect of dapagliflozin is however independent of insulin. It has a low propensity to cause hypoglycaemia in healthy adults as the amount of glucose excreted is dependent on the blood glucose concentration and glomerular filtration rate (GFR). Dapagliflozin also does not impair endogenous glucose production in response to hypoglycaemia.

Glucuresis induced with the use of dapagliflozin is also associated with caloric loss and it therefore offers the additional benefit of causing weight reduction, with the majority of this weight loss being body fat loss including visceral fat rather than lean tissue or fluid loss.

Indications

- As monotherapy with diet and exercise in patients with Type 2 Diabetes Mellitus for whom metformin is otherwise indicated but not tolerated
- In addition to diet and exercise as initial combination therapy with metformin to improve glycaemic control in patients with Type 2 Diabetes Mellitus when diet and exercise have failed to provide adequate glycaemic control or there are poor prospects for response to metformin monotherapy
- In combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control
- In combination with a sulfonylurea, when a sulfonylurea alone with diet and exercise does not provide adequate glycaemic control, and
- In combination with insulin (alone or with one or both of metformin or a sulfonylurea) when existing therapy, along with diet and exercise does not provide adequate glycaemic control.

Contraindications

In patients with known hypersensitivity to dapagliflozin or any of the tablet ingredients in Forxiga® and in patients with moderate to severe renal failure (CrCl< 60ml/min).

Precautions

Dapagliflozin should not be used in Type 1 Diabetes or for the treatment of diabetic ketoacidosis, in patients with severe hepatic impairment, and in pregnant or breastfeeding women.

Caution must be exercised with use of dapagliflozin in patients with mild renal impairment and it should not be used in patients with moderate to severe renal impairment.

Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted.

Dapagliflozin use has been associated with an increased risk of urinary tract infection, therefore temporary interruption of dapagliflozin should be considered while treating pyelonephritis or urosepsis. In cases of recurrent urinary tract infections, discontinuation of dapagliflozin should be considered.

Adverse effects

The most common side effects associated with the use of dapagliflozin are hypoglycaemia (especially when used in combination with add-on sulfonylurea and add-on insulin therapies), urinary tract infections, genital infections (more common in females), back pain, polyuria, dysuria, dyslipidaemia, nausea, headache, dizziness and rash.

Dosage and Administration

Dapagliflozin is available as 10mg tablets under the trade name of Forxiga® (Astra Zeneca and Bristol-Myers Squibb). The recommended dosage is 10mg taken once daily at any time of the day, regardless of meals.

No dosage adjustment is required for patients with mild renal or mild to moderate hepatic impairment. Renal function and the risk of volume depletion should be taken into account when using dapagliflozin in the elderly. Initiation of dapagliflozin in patients over the age of 75 years is generally not recommended.

PBS Information

Bristol-Myers Squibb Australia Pty Ltd made a submission to the *Pharmaceutical Benefits Advisory Committee (PBAC)* in March 2012 seeking an Authority Required (Streamlined) listing for dapagliflozin for the treatment of patients with Type 2 Diabetes in combination with insulin.

Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submission's clinical claim that dapagliflozin (in combination with insulin) is non-inferior in terms of comparative effectiveness and comparative safety to pioglitazone (in combination with insulin).

The PBAC rejected this submission on the basis of an inadequate comparison across appropriate comparators and uncertain comparative clinical effectiveness.

As a result of this decision, dapagliflozin is currently not PBS listed. However, given the amount of interest that the SGLT2 receptor antagonists are generating as a treatment option for Type 2 Diabetes, it would be worthwhile watching this space.

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Vaccination Trends in Australia: Strength in Numbers

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"Protect your world – get vaccinated." That's the message that the *World Health Organisation (WHO)* hopes to spread. However, in Australia an old debate has been reignited surrounding a parent's right to choose whether or not to vaccinate their child. Dr Steve Hambleton, President of the *Australian Medical Association*, has suggested that parents who choose not to vaccinate their children should be penalised and even face difficulties in enrolling their children at school.

These comments come in the wake of new data which indicates that immunisation rates are falling across Australia. The national average of babies who are fully vaccinated stands at around 92%, one of the highest rates in the world. However, there is wide variation across the country. For example, the number of one-year-olds fully vaccinated in Eastern Sydney stands at 84%, whilst the Great South Coast region of Victoria boasts a more impressive rate of 95%.

The significance of this geographical disparity would imply that a sizeable proportion of the Australian public are not protected by herd immunity. Herd immunity can be described as the level of disease resistance of a community or population. In a population with high levels of immunity to a contagious infection, the introduction of that pathogen will result in lower levels of infection than it would if it were introduced to a population with less immunity. In effect, the immune status of the greater population has the ability to protect the few with no immunity to the introduced pathogen.

The notion of herd immunity is an important one to consider. Some members of the population either can't be fully immunised, or will have a less than ideal response to vaccines. This includes people who are taking immunosuppressants or chemotherapeutics, those with immunosuppressive illnesses, and those who are still too young to be fully vaccinated.

Unfortunately, it is these population groups; the very young and the very ill, who are often the most likely to suffer the more severe end of a disease's spectrum. In addition, there is always the fact no vaccine will be 100% effective.

The level of herd immunity required to effectively control the transmission of infection amongst a population varies for each disease. This threshold is dependent upon factors such as the virulence of the pathogen and the route of transmission. Diphtheria and rubella have a herd immunity threshold of around 85%, whereas pertussis has a threshold of up to 94%.

Thinking back to our national average vaccination rate of 92%, and allowing for the lower levels seen in places like Eastern Sydney, we can see that much of Australia is at risk of a pertussis outbreak, with many communities even falling short of the threshold required to halt the spread of diphtheria and rubella. Unfortunately, our disease notification rates reflect these figures with a staggering 34,793 pertussis notifications in 2010.

This alarming figure is one of the highest rates for pertussis notifications in the world. Despite having a pertussis vaccine on the childhood schedule for over 50 years, notifications have continued to increase over the past decade. Pertussis is highly contagious, as reflected by its high threshold for herd immunity.

To compound the problem, immunity provided by the pertussis vaccine wanes after 4-12 years.

Consequently, unless the entire population commits to regular boosters, herd immunity will not provide adequate protection against this disease.

Notification rates don't tell the whole story though, as current evidence shows that pertussis infections in those vaccinated generally result in less severe disease.

Other confounding factors in this upward trend in notifications could include improved detection methods and the emergence of a new genotype of *B. pertussis* which the vaccine provides poor protection against. Research into strategies to reduce the impact of pertussis in Australia is ongoing.

In the future we may see vaccine formulation changes, or changes to the recommended scheduling of vaccines.

It is worth noting that herd immunity is only relevant to contagious diseases. Tetanus, for example, is acquired from endospores which can be found in soil. As a result of this non-human reservoir of infection, it is only an individual's level of immunity – not the community's – that will provide protection.

The advantages of vaccination programs are abundantly clear; from the complete eradication of smallpox in 1979 to the current day where we teeter on the brink of a world free from polio. The *WHO* estimates that between two and three million lives are saved each year from vaccination alone.

Why are we seeing these declining trends in vaccination in a country like Australia, which

has one of the most accessible vaccination programs in the world and, more importantly, what can we do to help?

The decline in the rate of vaccination has been reported in the media to be due to the "Einstein Parent". These are the parents who question medical authority and often undertake extensive research of their own. In this day and age, the internet offers up a wealth of information, but also a wealth of misinformation. As health promotion is integral to the role of every healthcare professional, it is vital that we provide our patients with reliable information so that the choices they make are informed ones.

To do this we must understand the barriers to vaccination. There have been a considerable number of myths perpetuated by anti-vaccination lobbyists. The Australian Government produces an excellent resource to address these myths entitled, *"Immunisation Myths and Realities: Responding to Arguments Against Immunisation"*. This booklet is available to download from the *Department of Health and Ageing* and I would encourage all healthcare professionals to be familiar with its contents.

In addition to the fear-mongering employed by the anti-vaccine camp, there also appears to be a general sense of complacency surrounding many of the serious infections on the vaccination schedule. With the last polio outbreak recorded in Australia in 1956, a parent could be forgiven for thinking that it is unnecessary to protect their child from such an obscure threat.

The same could be said for diphtheria which is virtually unheard of in Australia. However, while these diseases are still active in the world, the risk of coming into contact with "obscure threats" is really only a plane trip away. The death of a 22-year-old Australian woman from diphtheria in 2011 highlights this point particularly well. She was not vaccinated against diphtheria and contracted the disease in Australia from a friend who had recently returned from overseas.

Like any medication, vaccines do have side effects and these should be discussed honestly with patients or their carers. It should be reiterated that the vast majority of these side effects are minor and temporary in nature. Whilst some may argue that it is not ethical to expose a healthy individual to *any* side effects, vaccination remains one of the most effective means of reducing disease burden. The effectiveness of vaccines in reducing disease is second only to clean drinking water, access to which is considered a basic human right.

Many of the reasons for the declining trends in vaccination rates can be addressed through education and understanding. I would urge you all take the time to acquaint yourselves with some of the common barriers to vaccination. At the same time, it wouldn't hurt to evaluate our own immunisation statuses, particularly those of us with patient contact.

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Management of Postoperative Nausea and Vomiting

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Introduction

Postoperative nausea and vomiting (PONV) is defined as nausea and/or vomiting which occurs within 24 hours after surgery. It is the most common and undesirable side effect following surgery and affects between 20-30% of patients. However, 70-80% of high risk patients may be affected. PONV results in increased patient discomfort, costs related to delayed hospital discharge, and could also lead to serious medical complications such as pulmonary aspiration of gastric contents, or fluid and electrolyte disturbances.

Risk Factors

The aetiology of PONV is thought to be multi-factorial. They can be divided into three main groups; patient specific factors, anaesthetic agents, and the type of surgery performed. A patient who is a female non-smoker, with a history of PONV or motion sickness, has a greater need for PONV medication. The use of intra-operative and postoperative opioids, nitrous oxide, volatile inhalational anaesthetics (ether), and some intravenous anaesthetics (ketamine, etomidate) are associated with an increase in PONV. Certain types of surgeries such as plastic (breast), gynaecological, ophthalmic (strabismus repair), ENT, laparotomy, laparoscopy and craniotomy are also known to predispose to PONV.

Pharmacological Prevention and Treatment of PONV

Prophylaxis isn't generally indicated in low-risk patients, single drug prophylaxis is appropriate for moderate-risk patients, and multiple intervention prophylaxis is reserved for high-risk patients. Apfel *et al.* developed a simplified risk score consisting of four predictors for PONV.

There are four major receptor systems involved in the aetiology of PONV. Current available antiemetics may act at the cholinergic (muscarinic), dopaminergic (D2), histaminergic (H1), or serotonergic (5HT3) receptors.

Serotonin (5HT3) Receptor Antagonists

Ondansetron was the first drug of this class, and is still the most commonly used. Others include granisetron, tropisetron and dolasetron. They produce pure antagonism of the 5HT3 receptor. Gan *et al.* found that there was no evidence of any difference in the efficacy and safety profile of the different 5HT3 receptor antagonists in the prophylaxis of PONV. Ondansetron is well tolerated with few adverse effects; headache, light-headedness, dizziness, elevated liver enzymes, and constipation being the most commonly reported. Studies have shown that intravenous ondansetron 4-8mg given at the end of surgery is significantly better than before induction of anaesthesia in treatment of PONV.

Granisetron is more selective than ondansetron, and a low dose of 1mg given intravenously is effective in the prevention and treatment of PONV. The elimination half-life is nine hours, about two and a half times longer than ondansetron, and so may require less frequent dosing. However, its high cost limits its clinical application.

Dolasetron is a highly potent selective serotonin receptor antagonist. The recommended intravenous dose of dolasetron is 12.5mg given 15-30 minutes before the end of surgery. Dolasetron is metabolised into hydrodolasetron, which has an elimination half-life of approximately eight hours and is 100 times more potent.

Tropisetron has a longer elimination half-life of 8-12 hours compared to ondansetron. Alon *et al.* reported intravenous tropisetron 2mg may be effective against PONV in most surgeries. Intravenous tropisetron 5mg before the anaesthesia has been found to be effective for PONV of breast and gynaecological surgery.

Droperidol

Droperidol acts competitively on central dopaminergic receptors, and side effects include sedation, drowsiness (dose dependent), dysphoria, restlessness, and extrapyramidal reactions (rarely). *Ku* and *Ong* stated that intravenous low doses of droperidol 0.625-1.25mg have been shown to be as effective as ondansetron 4mg without increasing sedation, agitation or anxiety.

According to *Kovac*, numerous studies have shown that droperidol and ondansetron are similarly effective in preventing PONV in adults. However, a "black box" warning issued by the *U.S Food and Drug Administration* about droperidol states that it may cause death associated with prolonged QT interval and increased risk of Torsades de Pointes.

Metoclopramide

Metoclopramide is a benzamide prokinetic agent with dual sites of action, blocking the dopamine receptors in the gastrointestinal tract and centrally in the chemoreceptor trigger zone. It also antagonises

serotonin receptors at high doses. Metoclopramide increases the lower oesophageal sphincter tone and facilitates gastric emptying into the small intestine. Opioid-induced PONV can be treated with metoclopramide because it reverses the gastric stasis induced by morphine. Metoclopramide is best reserved for use pre or postoperatively in those procedures where there is evidence for delayed gastric emptying, or, for patients at risk of gastro-oesphageal reflux.

Extrapyramidal side effects such as akathisia, acute dystonia, pseudoparkinsonism and tardive dyskinesia can occur. It is not recommended following gastrointestinal surgery involving anastamoses. In a meta-analysis performed by Domino *et al.*, metoclopramide has been shown not to be as effective as ondansetron and droperidol for prophylaxis of PONV.

Phenothiazines

Promethazine and prochlorperazine exert a direct dopamine 2 receptor antagonism effect in the chemoreceptor trigger zone with moderate antihistaminergic and anticholinergic actions. Promethazine is an effective prophylactic antiemetic, although less effective than prochlorperazine, and with more sedation, more prolonged recovery period from anaesthesia, and higher incidence of extrapyramidal side effects. Both agents are believed to be effective in the treatment of opioid-induced PONV, but their use as the primary treatment of PONV is limited by their tendency to cause sedation.

Neuroleptic malignant syndrome (catatonia, cardiovascular instability, hyperthermia and myoglobinaemia mortality in excess of 10%) has been reported with prochlorperazine, promethazine, droperidol, and metoclopramide.

Other Agents

Dexamethasone, a corticosteroid administered intravenously at a dose of 8-10mg has been shown to be an effective prophylaxis for PONV. The mechanism of action is still uncertain, however its long duration of action and cost-effectiveness makes it an attractive first line treatment. Unfortunately, it has no role in the treatment of established nausea and vomiting. Early administration is required due to its slow onset of action (peak effect at 1-2 hours).

Henzi *et al.* reported that when there is a high risk of postoperative nausea and vomiting, a single prophylactic 8-10mg dose of intravenous dexamethasone is effective compared with placebo. Dexamethasone has been shown to be more effective when it is used in combination with other antiemetic agents (ondansetron or dolasetron) than when it is used as a single agent.

Combination Therapy

Some studies have shown repeating a second dose of a single agent is unlikely to increase efficacy. In fact, in addition to increasing the cost, it is likely to increase the risk of side effects. It is reasonable to choose additional agents with a different mechanism of actions, as a combination should be more effective than a single agent alone in inhibiting the complex emetic reflex. Combination therapy should be reserved for when a single agent is ineffective, and for those patients at high risk of PONV.

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Systemic Antifungals

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Fungal Infection Overview

Fungi can be found in many places including in soil, plants, on our skin, and in our bodies.

A 'primary' fungal infection (mycosis) occurs in immunocompetent patients, where 'opportunistic' infections are not usually pathogenic, and affect immunocompromised patients. The incidence of such infections is rising due to an increasing number of patients who are immunocompromised.

Many local fungal infections can be treated topically. If the infection isn't able to be treated locally, does not resolve with local treatment, or if the patient is immunocompromised, then systemic treatment may be required.

Azole Antifungals

(Fluconazole, Itraconazole, Ketoconazole, Posaconazole and Voriconazole)

Azoles are fungistatic and break down fungal cell membranes by impairing synthesis of ergosterol, leading to fungal cell leakage; and then death from the lytic activity of the patient's immune system. They can be used for a wide range of fungal infections and for most agents the dose, frequency and duration are dependent on the indication.

They can interact with a wide range of drugs, particularly those metabolised by cytochrome P450 enzymes. In particular azoles should not be administered to patients taking cisapride. Patients with hypersensitivity to an azole should only cautiously be prescribed a different azole due to the possibility of cross-reactivity.

Fluconazole and voriconazole can cause prolonged QT interval and increase the risk of arrhythmias, and itraconazole can precipitate or worsen heart failure, so these three azoles should be used with caution in patients with cardiovascular disease. Azole side effects are individual to each drug. Broadly speaking, the commonly occurring side effects with azole therapy are: rash, gastrointestinal (GI) upset, headache and elevated liver enzymes. Long term use of azoles can lead to worsening of peripheral neuropathy.

Monitoring of azoles depends on the agent used. In general the serum potassium concentration and liver function should be measured at baseline and repeated at regular intervals.

Echinocandins

(Caspofungin and Anidulafungin)

Echinocandins alter cell membrane permeability by inhibiting 1,3-beta-D-glucan synthase resulting in fungicidal activity against *Candida spp.* and fungistatic activity against *Aspergillus spp.*

Echinocandins are indicated for invasive candidiasis. Caspofungin is also used for oesophageal candidiasis, as empirical treatment of fungal infections in febrile neutropenic patients that don't respond to antibacterials, and as second line treatment of invasive aspergillosis.

Patients who are hypersensitive to one echinocandin should not be prescribed the other due to a risk of cross sensitivity.

Side effects commonly include GI upset, rash, hypokalaemia and raised liver enzymes. They can also cause infusion reactions such as fever, hypotension, flushing, chills, rash, itch, dyspnoea and bronchospasm. To minimise infusion reactions echinocandins should be infused slowly.

Amphotericin

Amphotericin causes fungal cell death by irreversibly binding to the ergosterol in the fungal cell membranes, altering the permeability of the membranes, leading to intracellular leakage.

Amphotericin is indicated to treat severe systemic fungal infections, cryptococcal meningitis, oral/perioral candidiasis, as prophylaxis of liver transplant and HIV patients, and as empirical treatment for febrile neutropenic patients who are unresponsive to antibacterials. Preparations of amphotericin include amphotericin lipid complex (Abelcet®) and liposomal amphotericin (AmBisome®).

Amphotericin can lead to renal impairment, particularly if used with other nephrotoxic drugs such as aminoglycosides. Adverse effects can commonly include infusion reactions, although these tend to lessen with continued therapy. To reduce the risk of an infusion reaction occurring an antihistamine or paracetamol can be administered, or the rate of infusion can be slowed. Other common side effects include hyperglycaemia, anaemia, hypoxia, increased alkaline phosphatase, increased serum bilirubin, tachycardia, and hyponatraemia.

Monitoring should include renal function, electrolytes, hepatic function and complete blood picture.

Flucytosine (5-FC)

Flucytosine is converted to fluorouracil in fungal cells. The fluorouracil undergoes phosphorylation resulting in inhibition of fungal DNA synthesis and also affecting protein synthesis by incorporating itself into fungal RNA.

It is only indicated to be used in conjunction with amphotericin to treat cryptococcal infections.

It should be used in combination with another antifungal because flucytosine has a narrow spectrum of activity and fungal resistance can develop quickly.

Flucytosine should be stored within a tight temperature range of 15-25°C because it can precipitate at low temperatures, and form fluorouracil above 25°C. Side effects commonly experienced include rash and GI upset. Thrombocytopenia, anaemia, leucopenia and elevated liver enzymes are dose related and are more common when the plasma concentration exceeds 100mg/L.

During treatment with flucytosine a baseline blood count, renal and hepatic function should be measured and then monitored regularly.

Griseofulvin

Griseofulvin acts by disrupting the microtubule function of the fungal cells.

Indicated when topical treatment has failed or is not appropriate in treating dermatophyte infections, it is contraindicated in lupus erythematosus (may exacerbate) and severe hepatic disease.

The dose and the duration of treatment depends on what part of the body is being treated. Tinea of the skin and hair should be treated for between four and six weeks but may be longer for areas with a thicker keratin layer. Infections of the nails should be treated for up to 12 months as the treatment should continue until the infected nail has grown out.

Side effects include headache, GI upset, photosensitivity, rash, blurred vision, confusion, dizziness, fatigue, and taste disturbance. Some people find that consuming alcohol during a course of griseofulvin can cause skin flushing and an increased heart rate, so alcohol consumption during therapy is not recommended.

Terbinafine

Terbinafine inhibits ergosterol synthesis via inhibition of squalene epoxidase which leads to the disruption of cell membranes and cell death. It is fungicidal to dermatophytes and fungistatic against *Candida albicans*.

It is indicated to treat onychomycosis and dermatophyte infections when topical treatment is ineffective or not appropriate. The duration of treatment is dependent on the condition being treated, usually between 2-12 weeks.

Do not use terbinafine in patients with active, chronic, and/or severe hepatic disease. Adverse effects commonly include headache, GI upset, itch and/or rash, urticaria, temporary elevation of liver enzymes, arthralgia and myalgia. Reversible taste disturbance may also sometimes occur. It may worsen psoriasis, and so should be used cautiously in these patients.

Pentamidine

Used to treat or prevent *Pneumocystis jiroveci (carinii)* pneumonia (PCP). Its mode of action isn't fully known and may include inhibition of the synthesis of protein, DNA, and RNA. It may also inhibit oxidative phosphorylation and has effects on the metabolism of folate. Pentamidine can interact with a wide variety of drugs.

Adverse effects are common and can be severe, with people suffering from AIDS more likely to be affected. Side effects are often encountered in the first week of intravenous treatment, possibly a result of accumulation of pentamidine in the tissues.

Side effects may present or persist weeks after the treatment has finished. Such side effects can include GI upset, taste disturbance, Stevens-Johnson syndrome, toxic epidermal necrolysis, confusion, dizziness, raised liver enzymes, nephrotoxicity, arrhythmias, hyper or hypo-glycaemia, pancreatitis, hypotension, electrolyte abnormalities, bronchospasm, thrombocytopenia or anaemia.

Side effects are less common with inhaled pentamidine, although it causes bronchospasm and cough, and should be used with caution in smokers or those suffering from asthma. A bronchodilator can be used prior to using the inhaled pentamidine to reduce this adverse effect. Inhaled pentamidine should not be used in patients suffering from active tuberculosis, because this increases the risk of transmission to others.

An ECG should be taken at baseline and regularly during treatment. Blood pressure, kidney and liver function, blood glucose, complete blood count, serum potassium, and serum calcium should all be monitored regularly during therapy.

Summary

Fungal infections requiring systemic treatment are often those that are hard to treat, fail topical therapy, or occur in immunocompromised patients. There are a broad range of systemic fungal conditions with an equally broad range of treatment options. Selection of an appropriate agent needs to account for the infection being treated, what agents have been used in the past, and other medications the patient is taking. Clinicians need to also ensure that an appropriate treatment duration is observed to ensure adequate resolution of the infection.

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

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Refresher of Thyroid Disorders

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Introduction

Thyroid disorders affect 1 in 10 Australians. The thyroid is an endocrine gland, located on the anterior sides of the neck that secretes hormones involved in metabolism, protein synthesis, and controlling calcium levels in the blood. Thyroxine (T4) is the major hormone secreted by the gland. Approximately 35–40% of T4 is transformed hepatically into, the four times more potent, triiodothyronine (T3) and a good portion is converted into inactive reserve T3 (rT3). The thyroid gland uses the essential micronutrient iodine to produce T4 and T3.

Thyroid activity is controlled by the hypothalamic-pituitary-thyroid feedback (HPT) system. The hypothalamus is stimulated by exogenous factors (such as cold or stress) or endogenous factors (low thyroid hormone levels) to secrete thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). TSH regulates the secretion of T4 which is converted to T3. High thyroid hormone levels will down regulate both TRH at the hypothalamus and TSH at the pituitary. Disorders are categorised by the abnormality of function; hypothyroidism (underactive thyroid) and hyperthyroidism (overactive thyroid).

Hypothyroidism

Hypothyroidism can affect almost all body systems and is characterised by a slowing down of processes due to deficiency of thyroid hormones. Hypothyroidism features include retardation of mental, cardiovascular, gastrointestinal, and neuromuscular systems. Symptoms that appear insignificant can include; low energy, depression, slow heart rate, cold intolerance, dry skin, hair loss, and constipation. More significant symptoms are muscle fatigue, weight gain, exacerbated heart failure, myxoedema (orange peel-like skin), and goitre. More frequently hypothyroidism is subtle; however it is crucial to identify it, to avoid a chronic and progressively lethal state.

Causes of hypothyroidism are; congenital (most common), iodine deficiency, autoimmune dysfunction (Hashimoto's disease), or anti-thyroid treatment. Hashimoto's thyroiditis is the most common cause of goitre in hypothyroidism. Hashimoto's disease is an autoimmune disease in which antibodies develop against thyroglobulin (binding protein for thyroid hormones) and thyroid peroxidase (enzyme involved in the production of thyroid hormones). These antibodies lead to decreased thyroid hormones and inflammation of the thyroid.

Hypothyroidism is treated using T4 replacement therapy with the aim to normalise TSH levels. Doses range from 25-200mcg depending on the patient's response. T4 replacement is very effective and non-compliance is the main source of treatment failure. T4 should be stored in the refrigerator, or up to 14 days at room temperature. Patients who use dose administration aids (Dosette®, Webster-pak®, etc) should be informed that these packs are preferably stored in the refrigerator. Adverse effects of T4 replacement are dose related and include cardiovascular effects (angina, tachycardia and arrhythmias), muscle cramps, restlessness, flushing, excessive weight loss and osteoporosis (all the signs of hyperthyroidism).

If left untreated hypothyroidism can eventually lead to somnolence, coma, and death. The treatment of hypothyroid coma is with a slow intravenous infusion of liothyronine sodium (T3) 20mcg once or twice daily and supportive therapy (heat conservation, intubation, prevention of adrenal insufficiency if needed). This dose form is available through the Therapeutic Goods Administration Special Access Scheme (SAS) and is reserved for when the patient is in a coma.

Hyperthyroidism (Thyrotoxicosis)

Excessive thyroid hormones will likewise affect organ systems conversely to that seen in hypothyroidism. This characteristically speeds up those organ system's activities. Signs and symptoms include irritability, rapid heart rate, excessive weight loss, heat intolerance, lid retraction and frequent bowel motions with increased appetite. Goitre, though very uncommon, may exist in hyperthyroidism. More common symptoms are subclinical and, if left untreated, patients have an increased risk of developing cardiac arrhythmias, heart failure, and osteoporosis.

Pathology Result	High T4	Normal T4	Low T4
High TSH	Possible adenoma and/or thyroxine resistance	Early or subclinical hypothyroidism	Primary Hypothyroidism
Normal TSH	Possible adenoma and/or thyroxine resistance	Euthyroid	Possibly secondary hypothyroidism
Low TSH	Hyperthyroidism	Subclinical hyperthyroidism	Secondary hypothyroidism

Table 1. Diagnosis Matrix to Interpret Thyroid Pathology.

Thyroid storm is however, an uncommon although serious condition that may arise from subclinical hyperthyroidism exacerbated by another acute condition (surgery, childbirth, infections, etc). In thyroid storm the metabolic abnormalities result in potential fever, cardiovascular compromise (hypertensive crisis, severe arrhythmia), and mental state changes requiring emergency intervention.

The most common causes of hyperthyroidism are Graves' disease, thyroid adenomas, ingested T4, and other medicines high in iodine content. Graves' disease is an autoimmune disease in which antibodies actually stimulate receptors found on the thyroid and result in goitre and over excretion of thyroid hormone. Less common is that these antibodies may actually block the receptors and result in hypothyroidism. Optical symptoms (retraction and spasm of the upper eyelid with that classic stare or frightened expression) are very common in Graves' disease.

Drugs that can induce hyperthyroidism should be reviewed in hyperthyroid patients. These include; iodides, amiodarone, lithium, interferon-alpha, and T4 overdose.

Diagnosis of thyroid disorders

Thyroid disorders are often diagnosed incidental to investigating causes of the individual's presenting complaint, because symptoms are often subclinical, or non-specific; therefore laboratory testing often occurs on a low index of suspicion. Blood pathology testing of serum T4, TSH (and to a lesser extent T3), thyroglobulin and antibody markers are necessary for diagnosis. The combination of results and the evidence of clinical symptoms will give an accurate indication of thyroid function.

Comparing TSH to T4 levels is usually the key to interpreting results as shown in Table 1. If the TSH level is high it can generally indicate dysfunction of the thyroid gland itself (primary hypothyroidism) and be treated as such. A low T4 level can indicate that either the thyroid is dysfunctional or the pituitary is not stimulating the thyroid. Low T4 levels should activate the HPT system, therefore if TSH levels are normal or low it could mean dysfunction of either the hypothalamus and/or pituitary (secondary hypothyroidism); so investigation, and correction, of the hypothalamus and/or pituitary should follow to avoid adrenal crisis.

A high T4 level alone is not always indicative of hyperthyroidism. Because T4 is just about totally protein bound and under certain physiological conditions (pregnancy, liver disease and oestrogen administration) thyroglobulin levels are increased, moderately increasing T4 level results. Also low TSH does not necessarily indicate hyperthyroidism and may be evidence of an injured pituitary. Therefore it is ideal to show both high T4 levels and low TSH levels to diagnose hyperthyroidism. High levels of T3 can be used for confirming diagnosis if TSH levels are low and T4 is in the normal range (T3 being more potent). Refer to Table 1.

Conclusion

Thyroid function has important consequences for other disease states and dysfunction may complicate treatment regimes of these diseases. Decreased thyroid function is treated with hormone replacement to allow re-establishment of the euthyroid (healthy) state, whilst increased function is treated by means to reduce hormonal levels either pharmacologically, surgically, or through radiotherapy. Diagnosis of subclinical dysfunction is through comparison of blood hormone levels.

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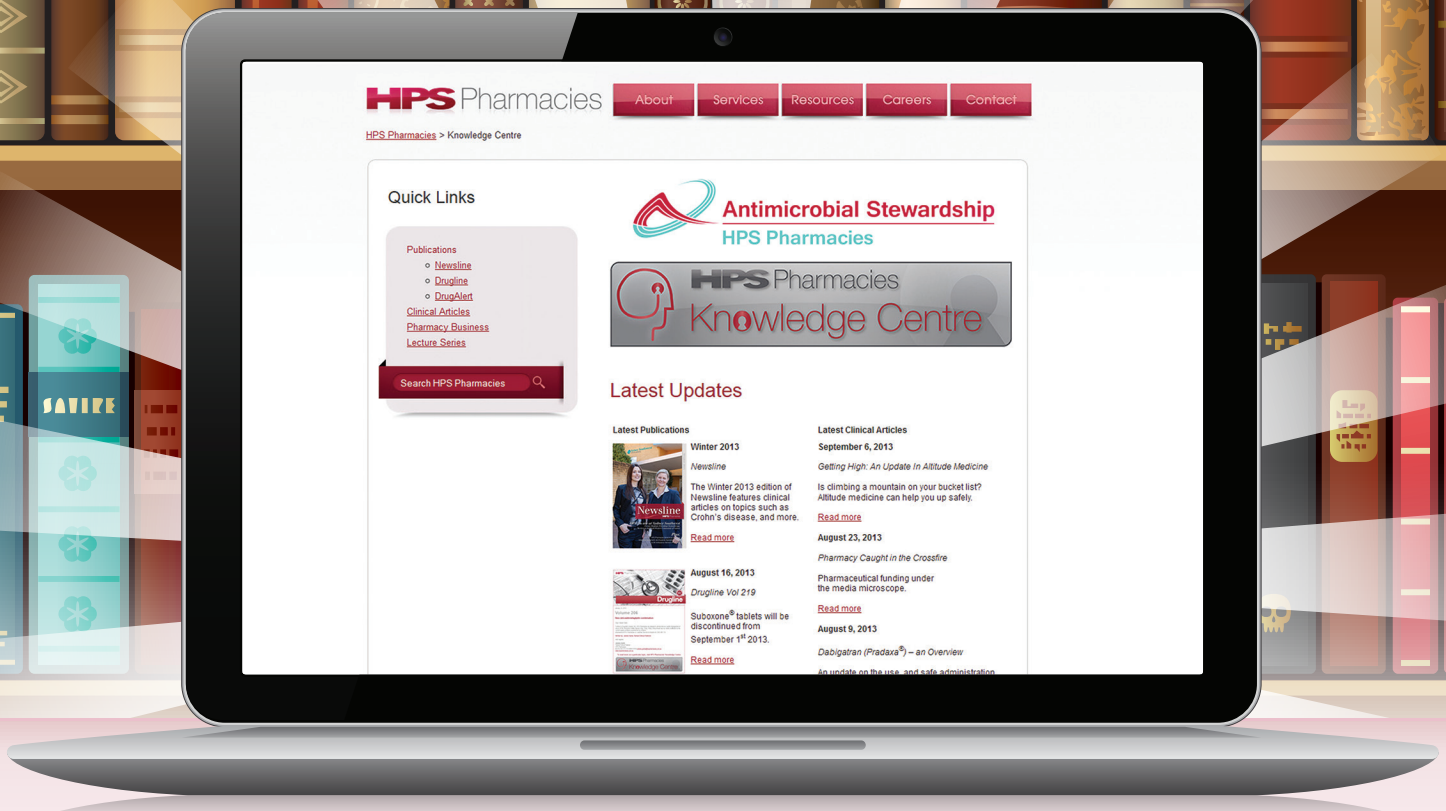

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