Adult liver transplantation: what non-specialists need to know

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The UK has approximately 6,000 surviving liver transplant recipients, and annually about 600 people with liver disease receive new livers. The post-transplant population is growing, since nearly 550 of those 600 patients are alive one year after the operation, and at least 300 are alive 20 years after. We review liver transplantation for a non-specialist audience, with an emphasis on transplants in adults.

Who needs a liver transplant?

Common triggers for referral in people with chronic, usually cirrhotic, liver disease are progressive jaundice, diuretic-resistant ascites, or hepatocellular carcinoma (box 1). Early referral is recommended since patients vary in their disease progression, and the assessment must be thorough. Liver transplantation is principally aimed at restoring health and improving survival, but, unlike other operations with similar potential benefit, limited resources restrict the number of people who receive transplants.

Evidence based criteria can statistically quantify the risk of death in patients with advanced liver disease. The Model for End-stage Liver Disease (MELD) score (which uses a formula based on measurements of bilirubin, creatinine, and International normalised ratio; www.unos.org/resources/MeldPeldCalculator.asp) accurately predicts short-term mortality. UKELD, the UK risk score, also predicts which patients are at risk of dying while on the waiting list, but, unlike other operations with similar potential benefit, limited resources restrict the number of people who receive transplants.

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Syndromes for which the mortality risk is not adequately reflected by such scores but which still portend a poor prognosis—such as diuretic resistant ascites—can also qualify an individual for transplant. However, there is little or no evidence that patients with other conditions, such as portopulmonary hypertension, fatigue, or pruritus, benefit in survival terms from transplant.

Transplants are also recommended for hepatocellular carcinoma that complicates cirrhosis, although cancer recurs in 10% of cases. Doctors are cautiously moving from restrictive size criteria (for example, offering transplant only to patients who preoperatively have either one tumour <5 cm or three tumours <3 cm), as recognition grows that the outcome is not always poor for those with larger tumour burdens. Chemoembolisation or targeted ablation therapy for patients who are already on the waiting list may improve the outcome, but there are few data from randomised trials to support this.

In acute liver failure, a rapid judgment commonly within a few days is required to identify the point at which survival with the recipient’s own liver is unlikely. The so-called King’s College criteria (a collection of clinical and laboratory parameters that predict death in acute liver failure, and thus potential benefit from transplantation) form the basis in the UK for “super-urgent” listing.

How are patients assessed for liver transplant?

Liver transplant assessment must answer three questions. Is there no alternative treatment for the liver disease? If the transplant is not curative, is the recurrence rate acceptable? And what are the unrelated medical conditions that will contribute to overall outcomes?

Most programmes seek a chance of survival of at least 50% at five years after the transplant. Few absolute contraindications for transplant remain. Transplants can be done at any age, although the outcome is less...
favourable for those over 65 years than it is for younger people. HIV infection is no longer a contraindication provided that the viral count is under control. Schizophrenia, depression, and previous alcoholism and drug abuse are not reasons to decline transplant, but co-morbidities that should be assessed. A six month abstinence rule applies to alcohol related disease to reduce recidivism as well as to allow for improvement in liver function with the hope of avoiding transplantation. Clinically harmful drinking post transplant is less prevalent than perceived, and only an estimated 6.5% drink heavily. Where live donor transplantation is contemplated, the healthy individual agreeing to a partial hepatectomy to donate a liver graft must undergo a detailed medical and social evaluation.

Transplant assessment meetings are multidisciplinary, and the process should be auditable. Patients who are refused transplantation after the first assessment are offered a second opinion. Nurse coordinators usually organise the assessment, which comprises a series of investigations and consultations, with particular focus on cardio-respiratory function. Since the average recipient is over 50 years old, cardio-respiratory concerns are common, and problems identified may lead to medical or surgical intervention before the patient is put on the transplant list. Smoking cessation is advocated for all. Nutritional evaluation for underweight or overweight people is important, since extremes of body mass index can be associated with poor perioperative outcomes. However, direct analysis of the data does not support exclusion based solely on weight. Limiting paracetamol sales, reducing transplant demand, and improving organ utility are ongoing challenges.

Ongoing Challenges

**Reducing transplant demand**
- Limiting paracetamol sales
- Screening and treating hepatitis C before end stage liver disease develops
- Alcohol harm avoidance programmes to reduce the burden of alcoholic liver disease

**Improving organ utility**
- Split liver grafting: improving surgical techniques to reduce complications
- Living donor transplantation to provide an alternative donor source
- Organ preservation strategies to increase donor numbers

**Increasing organ availability**
- Increasing numbers of donor coordinators who manage the donation process with bereaved families
- Professional training for coordinators
- Incentive schemes for intensive care units to increase donation

**Opt out** legislation—presumed consent to organ donation

**Optimising immunosuppression post-transplant**
- Monoclonal antibodies with the hope of greater specificity in immunosuppression
- Investigating role of chimerism in tolerance

**Alternative liver support/regeneration**
- Liver support devices equivalent to renal dialysis
- Stem cell/hepatocyte transplantation to reverse liver failure
- Gene therapy to treat chronic liver disease

**How long do patients wait for a transplant?**
In the UK, approximately 14% of all listed patients die or are considered too sick before a graft is available. Waiting times vary by country and reflect not only donor numbers, but also clinical caseloads, recipient weight and blood group as well as the organ listing or
**Systemic immunosuppression**
- a) Infection (local and systemic)
- b) Direct side effects especially renal, neurological, cardiovascular, bone
- c) Long term malignancy risk e.g. lymphoma, skin cancer

**Psychological adjustment**
- Reactive depression
- Family strain

**Liver parenchyma**
**EARLY**
- a) Primary non-function
- b) Acute rejection
- c) Ischaemia-reperfusion injury
- d) Impaired graft function secondary to anastomotic (biliary, vascular) complications
- e) Cut surface bile leaks in split livers

**LATE**
- a) Disease recurrence e.g. Hepatitis C, sclerosing cholangitis, alcohol, hepatocellular carcinoma
- b) Chronic rejection

**Hepatic veins to vena cava**
- Portal vein thrombosis/stenosis may lead to varices and pre-sinusoidal portal hypertension
- Hepatic artery
- Early hepatic artery loss (thrombosis) often leads to rapid liver failure
- Later hepatic artery loss (thrombosis/stenosis) usually presents with ischaemic biliary strictures

**Bile duct**
- Anastomotic strictures present with obstruction to biliary flow
- Leaks may present as sepsis; the proximity of the anastomosis to the artery means a leak may precipitate artery thrombosis
- Where the anastomosis is to bowel (Roux-En-Y) ascending cholangitis may also be seen

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**Schematic of potential complications of liver transplantation.**

Allocation strategies. The sickest patients benefit most from transplantation, even with a marginal graft, and prioritising patients according to a disease severity score has reduced waiting times in the United States. Adults in the UK on average wait 95 days (www.uktransplant.org.uk/ukt/newsroom/fact_sheets). Clinical management of patients on the waiting list aims to minimise new complications, such as diuretic precipitated renal failure, and necessitates the prompt treatment of infection. Surveillance for varices and hepatocellular carcinoma should continue while people are on the waiting list.

**What does the operation entail?**

Great progress in both liver surgery and liver transplantation has occurred as a result of improved preoperative diagnosis, and intraoperative and postoperative care. Hepatectomy, which is difficult with severe portal hypertension or when patients have had previous surgery, is followed by the anhepatic phase and liver implantation. Three important vascular anastomoses (inferior vena cava, portal vein, hepatic artery) are created to allow reperfusion. The biliary anastomosis can be done as duct-to-duct or as duct-to-small bowel.

The regenerative capacity of the liver means a whole liver is left in place), which may have utility in acute liver failure. The most frequent approach generates a left lateral and a right extended liver graft for donation to one child and one adult, respectively. In a potential extension of this approach, the liver can be split to provide two “full” hemi-grafts: the left side for a small adult or a large child and the right for a medium sized adult patient.

To maximise donor organ use, surgeons also accept livers with potentially more marginal outcomes such as with mild or moderate steatosis, from donors with previous hepatitis B exposure, and from those over the age of 65. The use of non-heart beating donors is increasing, although ischaemic biliary damage is a concern. Matching the graft size between donor and recipient is important, and matching for blood group is routine, except in acute liver failure, in which compatibility of blood groups is sufficient.

For living donors, the operation to remove a portion of their liver carries a significant mortality risk of 0.8%. Advantages for the recipient of having a living donor are elective surgery, a shorter waiting time and therefore a lower MELD at transplant, excellent donor liver function, and minimal cold/warm ischaemia. However, vascular and biliary complications are increased, along with a potential for “small-for-size syndrome”.

**What are the potential complications of transplantation?**

Although symptoms and post-operative examination can identify concerns, the complexities of the surgery and the consequences of immunosuppression mean there is a heavy reliance on blood tests, imaging, and liver biopsy to identify complications (figure). The

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**A PATIENT’S PERSPECTIVE**

In retrospect, I realise that low level confusion had already set in probably before I was admitted to hospital. I was “liver ignorant,” had heard the liver could regenerate and was due on holiday in 2 weeks—plenty of time to get rid of the jaundice! Little did I appreciate that my liver was failing and I would need a transplant for a condition I had never heard of (“seronegative acute liver failure”). I didn’t understand the magnitude of it, but I wasn’t frightened. I just felt profoundly sad at the potential consequences for my family.

After the transplant in the intensive care unit, I was spoken to frequently, and my emotions were up and down. The nurses were a lifeline. I did go through a phase of thinking I might not be one of the lucky ones to get better, but I went back to a normal life. Having people take the time to listen to me, explain things patiently, and talk to my family meant a lot. A liver transplant is not an experience you would choose for yourself or your family, but there are worse things. Aside from returning my health, it has restored my faith in human nature. It is a cliche but I will never be able to thank my donor (or their family) enough as well as all those involved, not just doctors, and not just those at the transplant centre.

Lorna Bailey
immediate postoperative period is often uneventful, but problems can include bleeding or poor graft function. Early postoperative patients can develop sepsis, difficulties with vascular and biliary anastomoses, and acute graft rejection. In the late postoperative period, the consequences of immune suppression (such as renal impairment, cardiovascular risk, and malignancy) and disease recurrence are more frequent than chronic graft rejection.

Common sites of infection are the chest, urine, blood, abdomen, and indwelling cannulae. Short term prophylaxis is given according to local guidelines and can include valgancyclovir for cytomegalovirus, fluconazole for fungal sepsis, septrin for pneumocystis, and perioperative broad spectrum antibiotics. Some patients may need prophylaxis against a reactivation of tuberculosis. The transmission of unusual infections, such as rabies or arenaviruses, through liver donation, however, is very rare.

Acute cellular rejection is common (roughly estimated at 25-30%), and, since patients are reviewed regularly in the early post-transplant period, it is usually identified when asymptomatic, as a result of abnormal blood tests (such as, raised liver enzymes, bilirubin, or eosinophil count). Non-specific symptoms such as lethargy, fever, and abdominal pain may be presenting features, but there are no specific symptoms or signs. The target tissues include bile ducts and hepatic vascular endothelial cells, and liver biopsy is usually used to grade severity and exclude alternative pathologies (such as sepsis, recurrent disease, ischaemia, or drug toxicity). Moderate or severe rejection is treated with methylprednisolone, usually without incident. Chronic rejection, which usually occurs only after the first year, is different; it is sometimes referred to as “vanishing bile duct syndrome” because of the progressive loss of the bile ducts. Histological tests often show a vasculopathy of the main branches of the hepatic artery. Risk factors include those with previous acute rejection, and a recent change in immunosuppression, including non-compliance. Patients can be identified through routine blood tests showing deranged liver enzymes (hepatitic or cholestatic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Side effects</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids, e.g. prednisolone (20 mg daily, tapering dose)</td>
<td>Synthetic corticosteroid with broad anti-inflammatory effects</td>
<td>Weight gain, hyperglycaemia, osteoporosis</td>
<td>Promotes replication of hepatitis B and C viruses</td>
</tr>
<tr>
<td>Azathioprine (1 mg/kg)</td>
<td>Purine synthesis inhibitor, inhibits cell proliferation</td>
<td>Marrow suppression, pancreatitis, veno-occlusive disease</td>
<td>Harmful interaction with allopurinol</td>
</tr>
<tr>
<td>Mycophenolate mofetil (up to 1 g twice a day)</td>
<td>Mycophenolic acid inhibits de novo purine synthesis by inhibiting inosine monophosphate dehydrogenase</td>
<td>Diarrhoea, marrow suppression, headache</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (target trough level 5-15 μg/L, depending on time since transplant)</td>
<td>Calcineurin inhibitor: macrolide antibiotic, inhibits T-lymphocyte signal transduction and interleukin-2 transcription</td>
<td>Nephrotoxicity, neurotoxicity (seizures or neuropathy), hypertension, diabetes</td>
<td>Reduces rate of chronic rejection in comparison to ciclosporin and is more reliably absorbed; NSAIDs may potentiate nephrotoxicity</td>
</tr>
<tr>
<td>Ciclosporin (target trough level 100-200 μg/L, depending on time since transplant)</td>
<td>Calcineurin inhibitor: inhibition of T-lymphocyte signal transduction and IL-2 transcription</td>
<td>Nephrotoxicity, neurotoxicity (seizures or neuropathy), hypertension, gum hypertrophy</td>
<td>May have activity against hepatitis C virus, and might reduce PBC recurrence rates; NSAIDs may potentiate nephrotoxicity</td>
</tr>
<tr>
<td>Rapamycin (target trough level 4-8 μg/L)</td>
<td>Inhibition of interleukin-2 receptor signalling (mTOR inhibitor)</td>
<td>Pneumonitis, atypical infection, impaired wound healing</td>
<td>Has anti-tumour and anti-fibrotic effects; stop treatment before elective surgery</td>
</tr>
<tr>
<td>Anti-lymphocyte and anti-thymocyte globulin</td>
<td>Lymphocyte depletion</td>
<td>Infection, serum sickness, lymphoma</td>
<td>Has a role in treatment of steroid-resistant acute rejection</td>
</tr>
<tr>
<td>Anti-CD25 monoclonal antibodies</td>
<td>Interleukin-2 receptor blockade</td>
<td>Hypersensitivity reactions</td>
<td>May allow delayed calcineurin inhibitor use in those with renal impairment</td>
</tr>
</tbody>
</table>

Box 2 Important interactions for those on tacrolimus, ciclosporin, or rapamycin

Inhibitors of the cytochrome P-450 system that can increase blood levels of immunosuppressants:
- Erythromycin, clarithromycin
- Clotrimazole, fluconazole, and ketoconazole
- Grapefruit juice
- Diltiazem, verapamil, and nicardipine
- Metoclopramide
- Ranitidine

Inducers of the cytochrome P-450 system that can decrease blood levels of immunosuppressants:
- Warfarin
- Carbamazepine, phenytoin, and phenobarbital
- Rifampin and rifabutin

NSAIDs = non-steroidal anti-inflammatory drugs, PBC = primary biliary cirrhosis
THE ROLE OF THE TRANSPLANT NURSE COORDINATOR

We have a varied but interesting role, from the first meeting with a potential recipient, continuing through the process of assessment, waiting, surgery and post-operative recovery. We often become well known to our patients, and the patients may confide in us things they don’t feel able to tell others. It is our responsibility to ensure that the patient and their family are fully informed about transplantation, including the ups and the downs, and the realities and risks.

Working alongside the whole team of doctors, nurses, pharmacists, and social workers, we ensure the patient undergoes the various tests and procedures needed to determine their suitability for transplantation. Being on the waiting list is a stressful and difficult period, and we help look after the physical and emotional needs of patients during this time. Our on-call role is largely enjoyable, as “setting up” a transplant for a patient who has been waiting anxiously on the list for some time is something special. This involves liaising closely with other members of the transplant team, including surgeons, anaesthetists, nurses and scientists. Sometimes it’s a “false start” and the patients all know that we won’t begin a transplant until the team is happy the organ is a good donation. It is extremely rewarding to see patients go on to have successful liver transplants, but also very sad and distressing when occasionally patients die while waiting for a liver or after a difficult transplant.

Seeing a patient return to health and being given a new chance of life is the best part of our role. It is crucial that we continue to support and educate the patient and their families through the post-operative course in order for them to leave hospital with confidence and looking forward to their future. It is important that they have trust in us as we are often the first member of the hospital team they contact if they have any questions or concerns about their health. We liaise closely with GPs and other health and social care professionals and like to know what’s happening to our patients, be it medical or social. Our relationship with our patients extends to seeing them in clinic not only at the transplant centre but increasingly in outreach clinics.

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Patterns), if they have non-specific symptoms, or present jaundiced with pruritus. Liver biopsy is mandatory for diagnosis, and immunosuppression is increased with the hope of restoring graft function, though not always successfully.

Immunosuppression requires several drugs (table). The goal is to use the lowest dose possible to maintain a healthy graft. Most doctors start with a combination of a calcineurin inhibitor, steroids such as prednisolone, and azathioprine. The role of specific monoclonal antibodies such as against the interleukin 2 receptor is yet to be established. Patients are then weaned off prednisolone (often by six weeks, though in some cases, such as in those with hepatitis C, it may be avoided entirely). Immunosuppression is subsequently either monotherapy, in the form of tacrolimus or ciclosporin, or dual therapy with additional azathioprine or mycophenolate. The largest study to date, a randomised controlled trial in the UK, compared the effectiveness of tacrolimus with that of ciclosporin, concluding that tacrolimus was associated with a better clinical outcome at one year. This finding was backed up by a subsequent Cochrane review that concluded that, compared with ciclosporin, tacrolimus was more effective at avoiding rejection and improving survival of the graft and the individual, although patients on tacrolimus were more likely to develop diabetes.

TIPS FOR GENERAL PRACTITIONERS

General concerns
Routine monitoring should include measurement of full blood count, renal function, liver biochemistry; frequency should be guided by time since transplant and clinical course

To monitor immunosuppression, levels of drugs such as tacrolimus, ciclosporin, and rapamycin are normally taken in the mornings before the drug dose; target values are generally managed by the transplant unit and drug doses usually lowered over time

For metabolic risk surveillance, monitor fasting lipids, glucose, uric acid, blood pressure; drugs usually needed include pravastatin, calcium channel blockers, and ACE inhibitors, though general health advice should emphasise need for exercise, smoking cessation, and low fat diet

Undertake surveillance for colon, cervix, breast, or skin cancer depending on sex and age

Vaccinate for influenza and pneumococcus, but avoid live vaccines and update patients on vaccinations for travel

Psychosocial support can be offered through support for alcohol or drug abuse; after transplant, some patients may need counselling or drug treatment (such as mirtazepine or citalopram) for depression or for help with adjusting to post-transplant life

Acute problems
Always consider the possibility of sepsis. Look at obvious sites first (such as chest, wound, urine). Look for viral rashes; consider abdominal source (for example cholangitis) and atypical sites such as mouth, sinuses, bones, heart, central nervous system. Immunosuppression might mask common symptoms such as fever, so normal white cell count does not exclude infection. Consider whether patient is at acute risk of adrenal suppression. Consider whether anything suggests a new malignancy, including lymphoma.

Renal impairment is common: avoid dehydration and potential drug toxicities (for example with calcineurin inhibitors, non-steroidals, or gentamicin)

Be quick to admit patients to, or ask for help from, their transplant unit

Rejection is rarely an out of hours concern and changes in liver biochemistry can be discussed with the transplant team: interpretation should be done in the context of baseline values and the underlying disease

Consider drug interactions carefully when prescribing drugs such as allopurinol, azathioprine, erythromycin, or tacrolimus.
What is the long-term outlook after transplant?

The quality of life after transplantation is good: for example, a recent long-term study found that patients who had survived for 10 or more years after transplantation had an average quality of life score of 24.5 (Ferrans and Powers questionnaire, mean Quality of Life Index score range 0 to 30), although some reported a reduced physical functioning after transplant.\textsuperscript{24}

The five year mortality is lowest in patients given transplants for primary biliary cirrhosis and highest in those with cancer. Second highest is in those given transplants for acute liver failure and hepatitis C cirrhosis.\textsuperscript{2} Although effective prophylaxis means that hepatitis B recurrence is rare, hepatitis C will recur if the patient is viraemic when they undergo the transplant.\textsuperscript{23} Many doctors will treat recurrent hepatitis C, accepting the risk of interferon precipitated rejection, because a sustained virological response offers a survival benefit. Other diseases that can recur include autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis (which can affect survival). Increasingly, both in people who have had transplants and those who have not, steatohepatitis is becoming common.

By five years post-transplant, 10-20% of patients may develop chronic renal failure, usually related to calcineurin inhibitor toxicity.\textsuperscript{26} Hypertension occurs in 60% of post-transplant patients (with half of these needing more than one drug for control) and diabetes in 35%.\textsuperscript{25} In one study, the incidence of developing diabetes after a transplant was one in five, which is twice that in non-transplant patients with hepatitis C.\textsuperscript{27} Obesity is nearly as frequent as hypertension; in one analysis, 21.6% of non-obese transplant recipients became obese over the 2 years after transplantation.\textsuperscript{28} Such metabolic disturbances broadly relate to the aetiology of the original disease, the side effects of immunosuppression, and post-transplant weight gain.

### What general practitioners need to do

The family doctor remains an important member of the team caring for transplant recipients, although their role is usually limited in the first year after surgery because the patient will need to visit the transplant team frequently. Later, when the family doctor assumes greater responsibility for hypertension, diabetes, hyperlipidemia, and cancer surveillance, advice is available from the transplant clinic.

Drug interactions are always important to consider (box 2). Management by the general practitioner should include lifestyle advice, aggressive treatment of hypertension (with calcium channel blockers, angiotensin pathway inhibition, α-receptor blockade), and screening for diabetes and hyperlipidaemia. Pravastatin, unlike other statins, does not interact with calcineurin inhibitors and is therefore the preferred treatment for hyperlipidaemia. Late mortality (> 5-10 years post-transplant) after liver transplantation is often a result of malignancy.\textsuperscript{29} Transplant brings a substantial increased incidence of almost all carcinomas, some of which are caused by pre-transplant risk factors—in particular alcohol—and others by long term immunosuppression. Common malignancies include skin, gastrointestinal, and lymphoproliferative disorders, so general practitioners should be proactive in advising against sun exposure and encouraging screening for breast, cervical, and colon cancer. The management of acutely unwell recipients is a common concern for non-specialists, but transplant clinics welcome discussion about sick patients at any time.

### Summary points

- Potential transplant recipients often outnumber donors.
- Improved donor schemes, broader donor criteria, split liver grafts, and live donors (who donate a portion of their liver) can increase the number of transplants.
- Long term survival after transplant is excellent.
- Family doctors are important in the management and monitoring of hypertension, diabetes, hyperlipidaemia, and renal function, and in cancer surveillance after the transplant.
- The prevention of end stage liver disease and the early detection of liver complications could reduce the number of transplants needed.

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### Additional educational resources

**Resources for healthcare professionals**
- UK Transplant website (www.uktransplant.org.uk/ukt)—Now known as the UK Directorate of Organ Donation & Transplantation, within NHS Blood and Transplant
- United Network for Organ Sharing (www.unos.org)—An American organisation that oversees organ donations across the United States
- American Association for the Study of Liver Diseases (www.aasld.org)—One of the leading professional organisations with the aim of preventing and curing liver disease
- The National Liver Transplant standards (www.ncg.nhs.uk/documents/ns_national_professional)
- European Liver Transplant Registry (www.eltr.org)—A network of European liver transplant centres that aims to register all transplants in Europe
- British Liver Trust (www.britishlivertrust.org.uk)—A charity providing information and support for people with liver disease
- American Liver Foundation (www.liverfoundation.org)—A charity that advocates and promotes education, support, and research for the prevention, treatment, and cure of liver disease
- Liver transplant support (www.livertransplantsupport.co.uk)—A patient support website
- Addenbrooke’s Liver Transplant Association (www.alta.org.uk)—A long standing patient run liver transplant association.

*All these websites are free and do not need registration.

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From our archive

Treating hypertension with propranolol (1964)

Fifteen out of 16 hypertensive patients given propranolol for up to seven months have shown reductions of blood-pressure. Propranolol alone may prove to be useful in the treatment of mild and moderately severe cases of hypertension. In one patient experiencing marked drowsiness on methyldopa a change to propranolol resulted in improved blood-pressure control with no side-effects. Propranolol produced a considerable hypotensive effect in patients on adrenergic neurone-blocking and milder hypotensive drugs.

Propranolol has so far proved relatively free from side-effects and patients usually feel well on the drug. We have seen one case where heart failure was precipitated by propranolol; this has been reported following pronethalol (Stock and Dale, 1963). We consider that propranolol should be used with great caution, if at all, in patients with a history suggestive of heart failure, though one such patient with severe angina responded well without trouble. The only other side-effect in the dosage recommended for the treatment of hypertension, up to 200 mg. a day in divided dosage, has been slight tiredness in 2 of the 23 patients, readily relieved by reduction of the dosage. The side-effects seen with large doses used in our angina trial have also been relieved by reducing the dose.

While a central mode of action is not excluded it is suggested that beta-receptor-blocking drugs exert their hypotensive action by blocking the sympathetic receptors in the heart.


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